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ITEM

Literature Search for DDT and DDE

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OBJECTIVE

1. A Literature search was performed in November 2011 covering the years 2010 and 2011. The purpose of this search was to identify new Literature (mainly focusing on *p,p'*-DDT and *p,p'*-DDE) which may be applicable to update the Environmental Health Criteria 241 (DDT in indoor residual spraying: human health aspects) as published by the WHO in 2011, which reflects the relevant Literature until November 2010.

For the search as presented in this paper, the bibliographic Database SCOPUS was used. Search terms were (Toxicolog* OR Epidemiolog* OR human exposure) AND DDT. A further search was performed early December 2011 with search terms as (Toxicolog* OR Epidemiolog* OR human exposure) AND (DDT OR DDE).

A total of 237 abstracts for both, 2010 and 2011, was obtained, from which 44 were selected and presented in the following as these were considered to be possibly relevant for the update.

These abstracts are presented in a format which included the Table of Contents running headers from the EHC 241 (2011) publication and its short summaries (framed and marked red).

Abstract essentials were highlighted.

2. A further search in the same mode was carried out on 12th of October 2012 covering the time 2011 through October 12, 2012. From a total of 384 abstracts found, 4 were selected for the year 2011 (those which had not been considered in the previous 2011 search) and 42 were chosen for the 2012 search period.

An updated SCOPUS search was performed covering the time October 13, 2012 through December 31, 2012. From a total of 23 abstracts, 5 were selected from this period.

Thus, this updated report now covers all relevant publications published in 2012 (or in press of 2012) that were identified to be significant.

3. A further search in the same mode was performed early October covering January through September 2013 and early December covering October and November 2013 in addition. Thus the entire search period was January 01, 2013 to the end of November 2013.

The search for this entire period provided a total of 130 abstracts for DDT+DDE or DDT and DDE alone respectively.

From these 130 abstracts, 51 were selected and marked red in this updated edition.

PART B—HAZARD AND EXPOSURE ASSESSMENTS

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2.1 Analytic	

Title: Development of dipstick-based immuno-chemiluminescence techniques for the rapid detection of dichlorodiphenyltrichloroethane (2012)

ABSTRACT: The occurrence of organochlorine pesticides in the environment has been a major concern, due to their high persistence and the possible impacts of their exposure to humans. Dichlorodiphenyltrichloroethane (DDT) is most hazardous and one of the most widely used organochlorine insecticides. DDT and its main metabolites are highly stable to physical, chemical and biological degradation and are therefore still being detected in many parts of the world. The present study describes dipstick-based immuno-chemiluminescence method for the detection of DDT with high sensitivity. Anti-DDT antibodies raised in chicken (IgY) were used as the biological sensing elements by immobilizing onto nitrocellulose membrane strips in a chemiluminescence (CL)-based dipstick technique. The photons generated during the biochemical interaction were directly proportional to the DDT concentration. A mean recovery of 81.2-95.6% was obtained for DDT-spiked fruit juice samples with 2.8-4.6% relative standard deviation (RSD). **Using the proposed dipstick-based immuno-CL method, DDT was detected with linearity in the range 0.05-1ng/mL, having a limit of detection (LOD) of 0.05ng/mL. This method can be used for the rapid, reliable detection of DDT pesticide.** (Baker 2012).

Title: Persistent organochlorine contaminants in hair samples of Northern Poland population (2012)

ABSTRACT: The concentrations of persistent chlorinated organic pollutants were determined in hair samples (n=40) collected from inhabitants of Northern Poland in 1968, 1989 and 2009 using gas chromatography ion-trap tandem mass spectrometry (GC-MS/MS). Among the analytes were β - and γ -isomers of hexachlorocyclohexane (β - and γ -HCH), dichlorodiphenyltrichloroethane (p,p'-DDT) and its metabolites (p,p'-DDE, o,p'-DDD, o,p'-DDT and p,p'-DDD) and 6 polychlorinated biphenyl (PCB) congeners (IUPAC Nos. 28, 52, 101, 138, 153 and 180). The following: p,p'-DDE, o,p'-DDT, p,p'-DDT and PCB congeners: 28, 52 and 101 could be quantified in all samples. Overall total organochlorines level was found to decrease in that order: 1968>1989>2009. The most significant time-dependent decrease was noticed for sum of mean values, Σ DDTs (1658, 143.9 and 36.5ngg⁻¹) and

Σ PCBs (42.2, 29.4 and 14.9 ngg⁻¹) while Σ HCHs (β -HCH and γ -HCH) were present at comparable levels (22.2, 9.8 and 12.6 ngg⁻¹) in 1968, 1989 and 2009 respectively. The highest concentrations of DDTs were found in samples from 1968. Despite the long storage time of samples, metabolites either parent compound p,p'-DDT are still present in those samples at very high concentrations. p,p'-DDE as the predominant and stable metabolite of DDT was detected in every sample in the highest concentration. A significant, continuous decrease of total concentration of all studied PCB congeners was observed over the studied period of time. **Current results confirm previous reports of other authors upon the utility of hair as an alternative matrix for evaluation of human exposure to persistent organic pollutants** (Wielgomas et al. 2012).

3. EXPOSURE SOURCES AND METRICS 31

3.1 Sources of exposure 31

Title: Bioaccessibility of pesticides and polychlorinated biphenyls from house dust: in-vitro methods and human exposure assessment (2012)

ABSTRACT: Semi-volatile chemicals like pesticides and polychlorinated biphenyls (PCB) tend to accumulate in house dust. This may result in residues of some parts per million (p.p.m.), closely associated with health impairments and diseases like cancer. To explain these associations, we must establish whether a relevant absorption from house dust into human organisms occurs, and most crucially the release of chemicals, that is, their bioaccessibility. Digestive as well as dermal bioaccessibilities were examined using in-vitro methods. On average, the digestive bioaccessibility was ~40% for the pesticides and ~60% for the PCB. The dermal penetration availability reached ~60% for the pesticides and ~70% for the PCB (percentages of the concentrations in the dust). Based on the bioaccessibility, an estimate of internal exposure was calculated and expressed as percentages of acceptable or tolerable daily intake (ADI/TDI) values. Exposure via the respiratory tract proved to be very low. Exposure via the digestive tract had maximum values of 4% for pesticides and 12% for PCB. **Dermal exposure was much higher. Even for average concentrations in house dust (≈ 0.5 p.p.m.), children exposed to DDT and PCB showed up to 300% of the ADI/TDI values, and adults about 60%. With high concentrations of contaminants in house dust, the maximum doses absorbed through the skin reached 5000% (Ertle and Butte 2012).**

Title: Risk assessment of bioaccessible organochlorine pesticides exposure via indoor and outdoor dust (2013)

ABSTRACT: Dust, enriched by dichlorodiphenyltrichloroethanes (DDTs), was defined as a new route of organochlorine pesticides (OCPs) exposure, especially for children. Chemical analyses showed the medians of Σ OCPs were 171 (outdoor) and 520 (indoor) μgkg^{-1} in Guangzhou (GZ) while 130 (outdoor) and 115 (indoor) μgkg^{-1} in Hong Kong (HK). Significantly higher accumulative effect of OCPs occurred in the size fractions of ≤ 63 and 63-100 μm than 100-280 and 280-2000 μm , therefore 0-100 μm dust particles were used for risk evaluation. Different cytotoxic effects on human hepatocellular live carcinoma cell (HepG2) and human skin keratinocyte cell line (KERTr) were found for extracts of indoor dust and outdoor dust from different functional areas. **For total exposure (dust and food), OCPs**

intake via dust was low for adults (accounting for 0.16-3.78% of total exposure), while for children it was high (8.16-24.4% of total exposure). Non-carcinogenic OCPs exposure via dust was safe for adults; however DDT and Dieldrin exposure for children was higher than Reference Dose (RfD). The cancer risk related to indoor dust exposure for GZ and HK was moderate, below 10⁻⁴, while 42% of residences in GZ should be of concern (10⁻⁵). However, when bioaccessible OCPs used, daily intake and health risk were found to be greatly lower than the estimates without considering bioaccessibility (Wang et al. 2013b).

3.1.1 Impact on changing over of insecticide

Title: Impact of changing over of insecticide from synthetic pyrethroids to DDT for indoor residual spray in a malaria endemic area of Orissa, India (2012)

ABSTRACT: Background & objectives: Development of insecticide resistance in malaria vectors has been a major problem for achieving effective vector control. Due to limited availability of insecticides, the only option is management of resistance by judiciously using the insecticides and rotating them to maintain their effectiveness. This study was carried out in a malaria endemic area of Sundergarh district in Orissa where synthetic pyrethroids (SP) were in use for the last couple of years. The change-over from SP to DDT was done in one arm of study, and the other two arms remained on SP and insecticide-treated nets (ITN). Entomological and parasitological monitoring was done to assess the impact. Methods: The study design comprised of three arms (i) two rounds of indoor residual spraying (IRS) with DDT 1g/m² as a change-over insecticide in areas previously under synthetic pyrethroids; (ii) two rounds of IRS with synthetic pyrethroid (alphacypermethrin, ACM) @ 25 mg/m²; and (iii) an unsprayed area under ITN/long lasting insecticide nets (LNs). Indoor residual spraying was undertaken under strict supervision to maintain quality and coverage. Contact bioassays were conducted to know the persistence of insecticide on sprayed surfaces and adult vector density was monitored in fixed and randomly selected houses. Malaria incidence was measured through fortnightly domiciliary surveillance under primary health care system in all the study villages. Results: The insecticide susceptibility tests showed that *An.culicifacies* was resistant to DDT but susceptible to malathion and ACM. However, *An. fluviatilis* was susceptible to all the three insecticides. ACM was effective in killing *An. culicifacies* on mud and wooden sprayed surfaces and maintained effective bioefficacy ranging from 92 to 100 per cent up to five months, whereas DDT failed to achieve effective mortality in *An.culicifacies*. However, there was significant decline in the density of *An.culicifacies* in ACM and DDT areas in comparison to ITNs/LNs. There was 61 per cent reduction in the slide positivity rate in ACM area in comparison to 48 and 51 per cent in DDT and ITN/LNs areas, respectively. The adjusted incidence rate of malaria cases per 1000 population in three study areas also showed significant declines within each group. Interpretation & conclusions: **The present findings show that the change-over of insecticide from synthetic pyrethroids to DDT brings about the same epidemiological impact as envisaged from continuing SP spray or distributing insecticide treated nets/long-lasting insecticidal nets provided there is a good quality spray and house coverage** (Sharma et al 2012) (2).

Title: Insecticide substitutes for DDT to control mosquitoes may be causes of several diseases (2013)

ABSTRACT: Malaria continues to be a public health problem in Bangladesh, despite efforts in the 1960s to eradicate the vectors through the use of DDT. At one point, eradication of malaria was acclaimed but later on it reappeared. The use of DDT is no more legally allowed in Bangladesh, which has been officially replaced by a number organophosphates and/or synthetic pyrethroids and their combinations in addition to the integrated vector management (IVM) package. IVM being a community approach is still to go a long way to be mass popular. Adulticides, larvicides, residual sprays, mosquito coil, insecticide-impregnated curtain, aerosol, etc. still serve as the major weapons of mosquito control. Thus, mosquito control still mostly depends on chemical insecticides. Although the use of DDT is banned in Bangladesh, there are reports on its illegal use in different forms. Moreover, there is tons of leftover DDT in Bangladesh, which is likely to cause several diseases. As per one report, about 500 MTs of DDT stockpiles are lying in the Medical Sub-Depots at Chittagong for over a period of 26 years. DDT is a persistent organic pollutant pesticide, which can cause diseases like cancer, endocrine disorder, disruption of immune system, embryonic abnormality, reproductive disorder, etc. **Other chemical insecticides, which are replacing DDT, are also not free of hazardous impacts. IVM thus appears to be a wise approach requiring concerted efforts for the management of mosquito to control malaria. Such an IVM comprises use of *Bacillus thuringiensis* Berliner var. *israelensis*, methoprene, biocontrol agents, cleaning of breeding sites, pyrethroid-impregnated curtain, etc. Therefore, a wise effort should be adopted to completely stop the use of DDT, eliminate its stockpiles wherever they are in Bangladesh and to popularise the IVM, not the chemicals-based alternatives throughout the country (Rahmann 2013).**

Title: Successful malaria elimination strategies require interventions that target changing vector behaviours (2013)

ABSTRACT: Background: The ultimate long-term goal of malaria eradication was recently placed back onto the global health agenda. When planning for this goal, it is important to remember why the original Global Malaria Eradication Programme (GMEP), conducted with DDT-based indoor residual spraying (IRS), did not achieve its goals. One of the technical reasons for the failure to eliminate malaria was over reliance on a single intervention and subsequently the mosquito vectors developed behavioural resistance so that they did not come into physical contact with the insecticide. Hypothesis and how to test it. Currently, there remains a monolithic reliance on indoor vector control. It is hypothesized that an outcome of long-term, widespread control is that vector populations will change over time, either in the form of physiological resistance, changes in the relative species composition or behavioural resistance. The potential for, and consequences of, behavioural resistance was explored by reviewing the literature regarding vector behaviour in the southwest Pacific. Discussion. Here, two of the primary vectors that were highly endophagic, *Anopheles punctulatus* and *Anopheles koliensis*, virtually disappeared from large areas where DDT was sprayed. However, high levels of transmission have been maintained by *Anopheles farauti*, which altered its behaviour to blood-feed early in the evening and outdoors and, thereby, avoiding exposure to the insecticides used in IRS. This example indicates that the efficacy of programmes relying on indoor vector control (IRS and long-lasting, insecticide-treated nets [LLINs]) will be significantly reduced if the vectors change their behaviour to avoid entering houses. Conclusions: Behavioural resistance is less frequently seen compared with

physiological resistance (where the mosquito contacts the insecticide but is not killed), but is potentially more challenging to control programmes because the intervention effectiveness cannot be restored by rotating the insecticide to one with a different mode of action. **The scientific community needs to urgently develop systematic methods for monitoring behavioural resistance and then to work in collaboration with vector control programmes to implement monitoring in sentinel sites. In situations where behavioural resistance is detected, there will be a need to target other bionomic vulnerabilities that may exist in the larval stages, during mating, sugar feeding or another aspect of the life cycle of the vector to continue the drive towards elimination** (Russell et al. 2013).

Title: Effect of Aedes aegypti exposure to spatial repellent chemicals on BG-Sentinel™ trap catches

ABSTRACT: Background: An integrated approach to reduce densities of adult *Aedes aegypti* inside homes is currently being evaluated under experimentally controlled field conditions. The strategy combines a spatial repellent (SR) treatment (applied indoors) with the Biogents Sentinel™ (BGS) mosquito trap positioned in the outdoor environment. In essence, when combined, the goal is to create a push-pull mechanism that will reduce the probability of human-vector contact. The current study measured BGS recapture rates of *Ae. aegypti* test cohorts that were exposed to either SR or control (chemical-free) treatments within experimental huts. The objective was to define what, if any, negative impact SR may have on BGS trap efficacy (i.e., reduced BGS collection). Methods. *Aedes aegypti* females were exposed to SR compounds within experimental huts in the form of either treated fabric (DDT and transfluthrin) or mosquito coil (metofluthrin). Test cohorts were released within individual screen house cubicles, each containing 4 BGS traps, following SR exposure according to treatment. Two separate test cohorts were evaluated: (i) immediate release (IR) exposed from 06:00-12:00 hours and released at 12:00 hours and (ii) delayed release (DR) exposed from 12:00-18:00 hours and released at 05:30 hours the following day. BGS recapture was monitored at 09:30, 13:30 and 15:30 hours and the cumulative recapture by time point quantified. Results: Exposure of *Ae. aegypti* females to either DDT or metofluthrin did not significantly impact BGS capture as compared to cohorts of non-exposed females. This was true for both IR and DR exposure populations. IR cohorts exposed to transfluthrin resulted in significantly lower BGS recapture compared to matched controls but this effect was primarily due to high mosquito mortality during transfluthrin trials. Conclusion: **Our data indicate no more than minor and short-lived impacts (i.e., reduced attraction) on BGS trap catches following exposure to the pyrethroid compounds transfluthrin and metofluthrin and no change in recapture densities using DDT as compared to matched controls. These findings suggest a combined SR and BGS approach to vector control could function as a push-pull strategy to reduce *Ae. aegypti* adults in and around homes** (Salazar et al. 2013).

Title: Contrasting patterns of tolerance between chemical and biological insecticides in mosquitoes exposed to UV-A (2013)

ABSTRACT: Mosquitoes are vectors of major human diseases, such as malaria, dengue or yellow fever. Because no efficient treatments or vaccines are available for most of these diseases, control measures rely mainly on reducing mosquito populations by the use of insecticides. Numerous biotic and abiotic factors are known to modulate the efficacy of

insecticides used in mosquito control. Mosquito breeding sites vary from opened to high vegetation covered areas leading to a large ultraviolet gradient exposure. This ecological feature may affect the general physiology of the insect, including the resistance status against insecticides. In the context of their contrasted breeding sites, we assessed the impact of low-energetic ultraviolet exposure on mosquito sensitivity to biological and chemical insecticides. We show that several mosquito detoxification enzyme activities (cytochrome P450, glutathione S-transferases, esterases) were increased upon low-energy UV-A exposure. Additionally, five specific genes encoding detoxification enzymes (CYP6BB2, CYP6Z7, CYP6Z8, GSTD4, and GSTE2) previously shown to be involved in resistance to chemical insecticides were found over-transcribed in UV-A exposed mosquitoes, revealed by RT-qPCR experiments. More importantly, toxicological bioassays revealed that UV-exposed mosquitoes were more tolerant to four main chemical insecticide classes (DDT, imidacloprid, permethrin, temephos), whereas the bioinsecticide *Bacillus thuringiensis* subsp. *israelensis* (Bti) appeared more toxic. The present article provides the first experimental evidence of the capacity of low-energy UV-A to increase mosquito tolerance to major chemical insecticides. This is also the first time that a metabolic resistance to chemical insecticides is linked to a higher susceptibility to a bioinsecticide. **These results support the use of Bti as an efficient alternative to chemical insecticides when a metabolic resistance to chemicals has been developed by mosquitoes** (Tetreau et al. 2013).

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Title: Human blood concentrations of dichlorodiphenyltrichloroethane (DDT) extrapolated from metabolism in rats and humans and physiologically based pharmacokinetic modeling (2010)

ABSTRACT: The present study defined a simplified physiologically based pharmacokinetic (PBPK) model for dichlorodiphenyltrichloroethane [1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane, DDT] in humans based on metabolic parameters determined in vitro using relevant liver microsomes, coefficients derived in silico, physiological parameters derived from the literature, and an established rat PBPK model is presented. The model consists of an absorption compartment, a metabolizing liver compartment, and a central compartment for DDT. Evaluation of the rat model was performed by making comparisons between predicted concentrations in blood and in vivo experimental pharmacokinetic values obtained from rats after daily oral treatment with DDT (10 mg/kg, a no-observed-adverse-effect level) for 14 days. Elimination rates of DDT in vitro were established from data from rat liver microsomes and from pooled human liver microsomes.

The results indicate that a simplified PBPK model for DDT is useful for a forward dosimetry approach in rats and/or humans and for estimating blood concentrations of other related compounds resulting from exposure to low chemical doses (Yamazaki et al. 2010).

Title: Toxicokinetics of dioxins and other organochlorine compounds in Japanese people: Association with hepatic CYP1A2 expression levels (2013)

ABSTRACT: Concentrations of persistent organochlorine compounds (OCs) including polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs) in the liver and adipose tissue of Japanese cadavers were measured, and their toxicokinetics were examined in association with hepatic cytochrome P450 (CYP) 1A protein expression levels. Total 2,3,7,8-tetrachlorodibenzo-p-dioxin toxic equivalents (TEQs) were 66 ± 74 and 65 ± 57 pg/g lipid weight (mean \pm S.D.) in the liver and adipose tissue, respectively. Total PCBs (sum of 62 congeners targeted), p,p'-dichlorodiphenyl-dichloroethylene (p,p'-DDE) and β -hexachlorocyclohexane (β -HCH) were detected at concentrations over 1 μ g/g lipid in both tissues of some specimens. For most of the dioxin-like congeners, total PCBs, p,p'-DDE, oxychlordane, α - and β -HCH, hexachlorobenzene (HCB), and tris(4-chlorophenyl)methane (TCPMe), age-dependent increases in concentrations were found in the adipose tissue of males. No such age-dependent trend was observed in the liver, suggesting that there are different mechanisms underlying the hepatic concentrations of OCs. Immunoblot analyses indicated detectable expression of hepatic CYP1A2 protein, whereas no CYP1A1 protein was detected. The CYP1A2 expression levels were positively correlated with concentrations (on wet weight basis) of 2,3,4,7,8-P5CDF, the dominant TEQ-contributed congeners in the liver, indicating the induction of this CYP. Hepatic CYP1A2 protein levels were strongly correlated with the liver to adipose concentration (L/A) ratios of PCDD/F congeners with more than 5 chlorine atoms. **Together with higher concentrations of the congeners in the liver than in the adipose tissue, the observation on L/A ratios of highly chlorinated PCDD/Fs suggests that induced hepatic CYP1A2 protein is involved in their sequestration in this human population, as observed in model animals (rodents). Nonetheless, the magnitude of hepatic sequestration (L/A ratio) of PCDD/Fs in this human population was lower than in other mammals and birds, reported previously. This study emphasizes the fact that toxicokinetics of some OCs can be affected at least partly by CYP1A2 protein levels in humans. For the extrapolation of their toxicokinetics from model animals to humans, knowledge on the induction and sequestration potencies of CYP1A is necessary (Watanabe et al. 2013).**

Title: Assessment of DDT relative bioavailability and bioaccessibility in historically contaminated soils using an in vivo mouse model and fed and unfed batch in vitro assays (2012)

ABSTRACT: In this study, DDTr (DDTr = DDT + DDD + DDE) relative bioavailability in historically contaminated soils (n = 7) was assessed using an in vivo mouse model. Soils or reference materials were administered to mice daily over a 7 day exposure period with bioavailability determined using DDTr accumulation in adipose, kidney, or liver tissues. Depending on the target tissue used for its calculation, some variability in DDTr relative bioavailability was observed; however, it did not exceed 25% (range 2-25%). When DDTr bioaccessibility was determined using organic physiologically based extraction test (Org-PBET), unified BARGE method (UBM), and fed organic estimation human simulation test (FOREhST) in vitro assays, bioaccessibility was less than 4% irrespective of the assay utilized and the concentration of DDTr in the contaminated soil. **Pearson correlations demonstrate a poor relationship between DDTr relative bioavailability and DDTr bioaccessibility (0.47, 0.38, and 0.28, respectively), illustrating the limitations of the static in vitro methods for predicting the dynamic processes of the mammalian digestive system for this hydrophobic organic contaminant (Smith et al. 2012).**

5. HEPATIC EFFECTS AND ENZYME INDUCTION

5.1 Laboratory animals and in vitro systems

5.2 Humans

Summary: In rats, at doses at and above 5 mg/kg bw per day, DDT caused liver enlargement. At similar and higher dose levels, DDT and DDE caused an increase in hepatic expression of a number of CYP enzymes. It has been demonstrated in rodents that *o,p'*-DDT, like phenobarbital, binds to CAR-PXR and induces xenobiotic metabolizing enzymes. None of the studies in humans indicated hepatotoxicity by the usual clinical chemistry. One occupational study suggested an effect on enzyme induction in the liver. Three studies in humans at levels greater than 50 µg/l serum, representing active use or occupational human exposure, noted an increase in GGT, but it is unclear whether this is an adaptive or adverse effect.

Title: Plasma levels of DDE/DDT and liver function in malaria control personnel 6 months after indoor residual spraying with DDT in northern Uganda (2010)

ABSTRACT: We investigated the relationship between plasma levels of dichlorodiphenyltrichloroethane (DDT) and liver function in malaria control personnel 6 months after one round of DDT indoor residual spraying (IRS). **Method.** This was a cross-sectional study in the districts of Apac and Oyam of Lango, northern Uganda. Volunteers were clinically examined, and 5 ml samples of venous blood were taken in heparinised tubes for a 6-month post-spray screening for DDT and plasma markers of liver function and internal organ disease. DDE/DDT was assayed using ELISA kits (Abraxis, USA); plasma enzyme activity concentrations of amylase, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transpeptidase (GGT) were analysed using routine clinical chemistry automated methods (Konelab, Vantaa, Finland). **Results.** All 96 plasma samples analysed for xenobiotics contained DDE/DDT in the empirical range of 24.00 - 128.00 parts per billion (ppb) with a mean (SD) of 77.00 (±26.00) ppb. All 119 plasma samples studied for the markers exhibited enzyme activity concentration values within the population reference ranges, with empirical means (SD) of amylase 71.86 (34.07), AST 23.83 (12.71), ALT 7.84 (10.01) and GGT 58.37 (62.68) µg/l. **Conclusion. Six months after IRS with DDT, the spray team had an average concentration of plasma DDE/DDT of 77 ppb. This had no deleterious effect on liver function. We recommend continued use of DDT for IRS disease control in Uganda until better practical alternatives are available** (Bimenya et al. 2010).

Title: Serum organochlorine pesticide residues and risk of gallstone disease: A case-control study in Xiamen (2012)

ABSTRACT: **Purpose:** To investigate the association between serum organochlorine pesticide residues and risk of gallstone disease. **Methods:** A 1:1, pair-matched, case-control study was designed. Data from 150 patients with gallstones diagnosed by abdominal ultrasonography at a single hospital from June 2009 to June 2010 were collected. A total of 150 patients without gallstones during the same period at the same hospital were recruited as the control group. Capillary gas chromatography was employed to measure the serum concentrations of dichlorodiphenyltrichloroethane (DDT) and hexachlorocyclohexane (HCH) residues. Multiple-factor conditional logistic regression analysis was conducted to estimate the relative risk of gallstones in relation to organochlorine pesticide residues in serum. **Results:** The percentages of *p,p'*-DDD and *o,p'*-DDT in serum of patients were significantly higher than those in serum of controls. The *p,p'*-DDE, α -HCH, and δ -HCH residues in serum of patients

were also significantly increased compared with those in serum of controls. Multiple-factor conditional logistic regression analysis showed that high levels of p,p'-DDE and p,p'-DDT residues were risk factors for gallstone disease. Conclusions: A high level of organochlorine pesticide residues in serum is a potential risk factor for gallstone disease, which suggests that environmental exposure to organochlorine pesticides should be evaluated with respect to gallstone formation (Su et al. 2012).

6. NEUROTOXICITY

Summary: DDT caused tremors and convulsions in mice and rats at doses above 6–8 mg/kg bw per day. Similar effects have been observed in children following acute accidental ingestion. No such effects have been reported for occupational and environmental exposure.

6.1 Laboratory animals and in vitro systems

6.2 Humans

Title: Prenatal organochlorine exposure and behaviors associated with attention deficit hyperactivity disorder in school-aged children (2010)

ABSTRACT: Organochlorines are environmentally persistent contaminants that readily cross the placenta, posing a potential risk to the developing fetus. Evidence for neurodevelopmental effects at low levels of these compounds is growing, though few studies have focused on behavioral outcomes. The authors investigated the association between prenatal polychlorinated biphenyl (PCB) and p,p'-dichlorodiphenyl dichloroethylene (p,p'-DDE) levels and behaviors associated with attention deficit hyperactivity disorder (ADHD), measured with the Conners' Rating Scale for Teachers (CRS-T), in a cohort of 607 children aged 7-11 years (median age, 8.2 years) born in 1993-1998 to mothers residing near a PCB-contaminated harbor in New Bedford, Massachusetts. The median umbilical cord serum level of the sum of 4 prevalent PCB congeners (118, 138, 153, and 180) was 0.19 ng/g serum (range, 0.01-4.41 ng/g serum). The authors found higher risk for ADHD-like behaviors assessed with the CRS-T at higher levels of PCBs and p,p'-DDE. For example, the authors found higher risk of atypical behavior on the Conners' ADHD Index for the highest quartile of the sum of 4 PCB congeners versus the lowest quartile (risk ratio = 1.76, 95% confidence interval: 1.06, 2.92) and a similar relation for p,p'-DDE. **These results support an association between low-level prenatal organochlorine exposure and ADHD-like behaviors in childhood** (Sagiv et al. 2010).

Title: In-utero exposure to dichlorodiphenyltrichloroethane and cognitive development among infants and school-aged children (2012)

ABSTRACT: BACKGROUND:: Dichlorodiphenyltrichloroethane (DDT) continues to be used for control of infectious diseases in several countries. In-utero exposure to DDT and dichlorodiphenyldichloroethylene (DDE) has been associated with developmental and cognitive impairment among children. We examined this association in an historical cohort in which the level of exposure was greater than in previous studies. **METHODS:** The association of in-utero DDT and DDE exposure with infant and child neurodevelopment was examined in

1100 subjects in the Collaborative Perinatal Project, a prospective birth cohort enrolling pregnant women from 12 study centers in the United States from 1959 to 1965. Maternal DDT and DDE concentrations were measured in archived serum specimens. Infant mental and motor development was assessed at age 8 months using the Bayley Scales of Infant Development, and child cognitive development was assessed at age 7 years, using the Wechsler Intelligence Scale for Children. **RESULTS::** Although levels of DDT and DDE were relatively high in this population (median DDT concentration, 8.9 µg/L; DDE, 24.5 µg/L), neither were related to Mental or Psychomotor Development scores on the Bayley Scales nor to Full-Scale Intelligence Quotient at 7 years of age. Categorical analyses showed no evidence of dose-response for either maternal DDT or DDE, and estimates of the association between continuous measures of exposure and neurodevelopment were indistinguishable from 0. **CONCLUSIONS:: Adverse associations were not observed between maternal serum DDT and DDE concentrations and offspring neurodevelopment at 8 months or 7 years in this cohort** (Jusko et al. 2012)

Title: Prenatal p,p'-DDE exposure and neurodevelopment among children 3.5-5 years of age (2013)

ABSTRACT: Background: The results of previous studies suggest that prenatal exposure to bis[p-chlorophenyl]-1,1,1-trichloroethane (DDT) and to its main metabolite, 2,2-bis(p-chlorophenyl)-1,1-dichloro-ethylene (DDE), impairs psychomotor development during the first year of life. However, information about the persistence of this association at later ages is limited. Objectives: We assessed the association of prenatal DDE exposure with child neurodevelopment at 42-60 months of age. Method s: Since 2001 we have been monitoring the neurodevelopment in children who were recruited at birth into a perinatal cohort exposed to DDT, in the state of Morelos, Mexico. We report McCarthy Scales of Children's Abilities for 203 children at 42, 48, 54, and 60 months of age. Maternal DDE serum levels were available for at least one trimester of pregnancy. Te Home Observation for Measurement of the Environment scale and other covariables of interest were also available. Results: After adjustment, a doubling of DDE during the third trimester of pregnancy was associated with statistically significant reductions of -1.37, -0.88, -0.84, and -0.80 points in the general cognitive index, quantitative, verbal, and memory components respectively. The association between prenatal DDE and the quantitative component was weaker at 42 months than at older ages. No significant statistical interactions with sex or breastfeeding were observed. **Conclusions: These findings support the hypothesis that prenatal DDE impairs early child neuro-development; the potential for adverse effects on development should be considered when using DDT for malaria control** (Torres-Sánchez et al. 2013).

Title: Prenatal exposure to environmental contaminants and behavioural problems at age 7-8 years (2013)

ABSTRACT: Animal studies showed that the developing brain is particularly sensitive to chemical exposure. Human studies carried out in areas with high exposures have proven neurodevelopmental disorders in relation to e.g. lead and PCBs. Whether these chemicals are associated with behavioural problems in childhood at current environmental levels is not well known. Therefore, we assessed the association between prenatal exposure to lead, cadmium,

PCBs, dioxin-like compounds, HCB and p,p'-DDE and behavioural problems in 7-8. year old children. Prenatal exposure data were obtained from the Flemish mother-new-born cohort. Lead, cadmium, PCBs, dioxin-like compounds, HCB and p,p'-DDE were analysed in cord blood. When the child reached 7-8. years, 270 mothers completed the Strengths and Difficulties Questionnaire assessing their children's behavioural health. We found that doubling the prenatal lead exposure (cord blood lead levels) was associated with a 3.43 times higher risk for hyperactivity in both boys and girls. In addition, total difficulties were 5.08 times more likely in the highest tertile for prenatal lead exposure compared to the lowest tertile. **In girls, total difficulties were 4.92 more likely when doubling cord blood p,p'-DDE, whereas no significant association was found in boys.** Further, we noted in boys a 1.53 times higher risk for emotional problems when doubling cord blood cadmium, whereas no significant association was found in girls. **These results indicate that the presence of environmental contaminants influences the mental health of the next generation** (Sioen et al. 2013).

Title: Evaluating the neurotoxic effects of lactational exposure to persistent organic pollutants (POPs) in Spanish children (2013)

ABSTRACT: Although the brain continues developing in the postnatal period, epidemiological studies on the effects of postnatal exposure to neurotoxic POPs through breast-feeding remain mostly inconclusive. Failure to detect associations between postnatal exposure and health outcomes may stem from the limitations of commonly employed approaches to assess lactational exposure. The aim of the present study was to assess whether lactational exposure to polychlorinated biphenyl-153 (PCB-153), dichlorodiphenyldichloroethylene (DDE), or hexachlorobenzene (HCB) as estimated with a physiologically based pharmacokinetic (PBPK) model, is associated with decrements in mental and psychomotor development scores of the Bayley Scales of Infant Development (BSID) test in children aged around 14-months of a subsample (N= 1175) of the Spanish INMA birth cohort, and to compare this with the effects of prenatal exposure. Although in the present study population PCB-153, DDE and HCB exposure increased within the first months of postnatal life, no associations were found between different periods of postnatal exposure to these compounds and mental or psychomotor scores. Increasing prenatal PCB-153 concentrations were associated with worse mental and psychomotor scores, although significance was only reached for psychomotor development (β [95%CI] = -1.36 [-2.61, -0.11]). **Indeed, the association between exposure and effects observed during prenatal life weakened gradually across periods of postnatal life. Results of the present study suggest that, although breastfeeding increases children's blood persistent organic pollutants (POPs) levels during postnatal life, deleterious effects of PCB-153 on neuropsychological development are mainly attributable to prenatal exposure** (Gascon et al. 2013b).

Title: Neuropsychological measures of attention and impulse control among 8-year-old children exposed prenatally to organochlorines (2012)

ABSTRACT: Background: We previously reported associations between organochlorines and behaviors related to attention deficit hyperactivity disorder among boys and girls at 8 years of age using a teacher's rating scale for a birth cohort in New Bedford, Massachusetts (USA).

Objectives: Our goal was to corroborate these findings using neuropsychological measures of inattentive and impulsive behaviors. Methods: We investigated the association between cord serum polychlorinated biphenyls (PCBs) and p,p'-dichlorodiphenyl dichloroethylene (p,p'-DDE) and attention and impulse control using a Continuous Performance Test (CPT) and components of the Wechsler Intelligence Scale for Children, 3rd edition (WISC-III). Participants came from a prospective cohort of children born during 1993-1998 to mothers residing near a PCB-contaminated harbor in New Bedford. Median (range) cord serum levels for the sum of four prevalent PCBs [congeners 118, 138, 153, and 180 (Σ PCB 4)] and p,p'-DDE were 0.19 (0.01-2.59) and 0.31 (0-14.93) ng/g serum, respectively. Results: We detected associations between PCBs and neuropsychological deficits for 578 and 584 children with CPT and WISC-III measures, respectively, but only among boys. For example, boys with higher exposure to Σ PCB 4 had a higher rate of CPT errors of omission [rate ratio for the exposure interquartile range (IQR) = 1.12; 95% confidence interval (CI): 0.98, 1.27] and slower WISC-III Processing Speed (change in score for the IQR = -2.0; 95% CI: -3.5, -0.4). **Weaker associations were found for p,p'-DDE.** For girls, associations were in the opposite direction for the CPT and null for the WISC-III. Conclusions: **These results support an association between organochlorines (mainly PCBs) and neuropsychological measures of attention among boys only. Sex-specific effects should be considered in studies of organochlorines and neurodevelopment** (Sagiv et al. 2012).

Title: Pesticide exposure and amyotrophic lateral sclerosis (2012)*

ABSTRACT: Our objectives were to summarize literature on the association of amyotrophic lateral sclerosis (ALS) with pesticides as a group and to evaluate associations of ALS with specific pesticides. We conducted a meta-analysis of published studies of ALS and pesticides as a group and investigated the association of ALS with specific pesticides, using data from the Agricultural Health Study (AHS), a cohort including 84,739 private pesticide applicators and spouses. AHS participants provided information on pesticide use at enrollment in 1993-1997. In mortality data collected through February 2010, ALS was recorded on death certificates of 41 individuals whom we compared to the remaining cohort (controls), using unconditional logistic regression adjusted for age and gender to calculate odds ratios (ORs) and 95% confidence intervals. In the meta-analysis, ALS was associated with use of pesticides as a group (1.9, 1.1-3.1). In the AHS, ALS was not associated with pesticides as a group, but was associated with use of organochlorine insecticides (OCs) (1.6, 0.8-3.5), pyrethroids (1.4, 0.6-3.4), herbicides (1.6, 0.7-3.7), and fumigants (1.8, 0.8-3.9). ORs were elevated for ever use of the specific OCs aldrin (2.1, 0.8-5.1), dieldrin (2.6, 0.9-7.3), DDT (2.1, 0.9-5.0), and toxaphene (2.0, 0.8-4.9). None of these associations was statistically significant. Similar results were observed in an analysis restricted to men. **In conclusion, the meta-analysis suggests that ALS risk is associated with use of pesticides as a group, and our analysis of AHS data points to OC use in particular. The latter results are novel but based on a small number of cases and require replication in other populations** (Kamel et al. 2012).

(* also referred to as **motor neurone disease**)

Title: Organochlorine pesticide levels and risk of Alzheimer's disease in north Indian population (2013)

ABSTRACT: Alzheimer's disease (AD) could result from a multifactorial process involving both genetic predisposition and exposure to environmental factors like pesticides. A case control study of 70 patients of AD and 75 controls was done to examine the association between organochlorine pesticides (OCPs) and risk of AD. OCPs (hexachlorocyclohexane (HCH), aldrin, dieldrin, endosulfan, pp'-dichlorodiphenyldichloroethylene (pp'-DDE), op'-DDE, pp'-dichlorodiphenyltrichloroethane (pp'-DDT), op'-DDT, pp'-dichlorodiphenyldichloroethane (pp'-DDD) and op'-DDD) were extracted from blood and quantitatively estimated using gas chromatography. A Mann-Whitney U test revealed significant difference in β -HCH levels ($U = 1237.00$, $W = 4087.00$, $z = -6.296$, $p = 0.000$, $r = -0.71$), dieldrin levels ($U = 1449.00$, $W = 4299.00$, $z = -5.809$, $p = 0.000$, $r = -0.68$) and pp'-DDE levels ($U = 2062.00$, $W = 4912.00$, $z = -2.698$, $p = 0.007$, $r = -0.59$) between AD patients and controls. **In conclusion, this study supports epidemiological studies that associate exposure to pesticides with increased risk of AD, and we identified the specific pesticides β -HCH, dieldrin and pp'-DDE that are associated with the risk of AD in the north Indian population. However, further research is needed to establish the potential role of these OCPs as an etiologic agent for AD case (Singh et al. 2013).**

7. IMMUNOTOXICITY 50

Summary: On the basis of the available data, it is not possible to conclude whether DDT or DDE exposures of adults are associated with immunotoxicity.

7.1 Laboratory animals and in vitro systems

7.2 Humans

7.2.1 Effect to peripheral blood mononuclear cells

Title: p,p'-DDE, a DDT metabolite, induces proinflammatory molecules in human peripheral blood mononuclear cells "in vitro" (2012)

ABSTRACT: In a recent study, our group demonstrated that when peripheral blood mononuclear cells (PBMCs) were treated "in vitro" with p,p'-DDE, a DDT metabolite, an antioxidant response and biomarkers of inflammation were induced at the mRNA level, indicating a proinflammatory state. Thus, the aim of this study was to evaluate the induction of proinflammatory molecules at the protein level in PBMCs exposed to p,p'-DDE "in vitro". **The main finding was that "in vitro" exposure to p,p'-DDE enhanced the expression of proinflammatory cytokines (TNF- α , IL-1 β , IL-6) at the protein level in PBMCs. We also observed COX-2 induction at the protein level. Considering that p,p'-DDE has been identified as a persistent metabolite and is frequently found in the population, it is important to evaluate early inflammation biomarkers in populations exposed to DDT and to estimate the true risk of inflammatory disease development (Cárdenas-González et al. 2012).**

Title: Dysregulation of cytokine response in Canadian first nations communities: Is there an association with persistent organic pollutant levels? (2012)

ABSTRACT: In vitro and animal studies report that some persistent organic pollutants (POPs) trigger the secretion of proinflammatory cytokines. Whether POP exposure is associated with a dysregulation of cytokine response remains to be investigated in humans. We studied the strength of association between plasma POP levels and circulating cytokines as immune activation markers. Plasma levels of fourteen POPs and thirteen cytokines were measured in 39 Caucasians from a comparator sample in Québec City (Canada) and 72 First Nations individuals from two northern communities of Ontario (Canada). Caucasians showed significantly higher levels of organochlorine insecticides (β -HCH, p,p'-DDE and HCB) compared to First Nations. Conversely, First Nations showed higher levels of Mirex, Aroclor 1260, PCB 153, PCB 170, PCB 180 and PCB 187 compared to Caucasians. While there was no difference in cytokine levels of IL-4, IL-6, IL-10 and IL-22 between groups, First Nations had significantly greater average levels of IFN γ , IL-1 β , IL-2, IL-5, IL-8, IL-12p70, IL-17A, TNF α and TNF β levels compared to Caucasians. Among candidate predictor variables (age, body mass index, insulin resistance and POP levels), high levels of PCBs were the only predictor accounting for a small but significant effect of observed variance (~7%) in cytokine levels. **Overall, a weak but significant association is detected between persistent organochlorine pollutant exposure and elevated cytokine levels. This finding augments the already existing information that environmental pollution is related to inflammation, a common feature of several metabolic disorders that are known to be especially prevalent in Canada's remote First Nations communities** (Imbeault et al. 2012).

7.2.2 Effect to Prostaglandin E2 in human trophoblasts

Title: Differential Effect of DDT, DDE, and DDD on COX-2 Expression in the Human Trophoblast Derived HTR-8/SVneo Cells (2012)

Abstract: The purpose of this study was to investigate the effect of 1,1,1-trichloro-2,2-bis-(chlorophenyl)ethane (DDT), 1,1-bis-(chlorophenyl)-2,2-dichloroethene (DDE), and 1,1-dichloro-2,2-bis(chlorophenyl)ethane (DDD) isomers on COX-2 expression in a human trophoblast-derived cell line. Cultured HTR-8/SVneo trophoblast cells were exposed to DDT isomers and its metabolites for 24 h, and COX-2 mRNA and protein expression were assessed by RT-PCR, Western blotting, and ELISA. Prostaglandin E2 production was also measured by ELISA. Both COX-2 mRNA and protein were detected under control (unexposed) conditions in the HTR-8/SVneo cell line. COX-2 protein expression and prostaglandin E2 production but not COX-2 mRNA levels increased only after DDE and DDD isomers exposure. **It is concluded that DDE and DDD exposure induce the expression of COX-2 protein, leading to increased prostaglandin E2 production. Interestingly, the regulation of COX-2 by these organochlorines pesticides appears to be at the translational level** (Dominguez-Lopez, P., Diaz-Cueto L. et al. 2012).

7.2.3 Effect to Prostaglandin E2 in rat ovarian granulosa cells

Title: Low Concentrations of o,p'-DDT Inhibit Gene Expression and Prostaglandin Synthesis by Estrogen Receptor-Independent Mechanism in Rat Ovarian Cells (2012)

Abstract: o,p'-DDT is an infamous xenoestrogen as well as a ubiquitous and persistent pollutant. Biomonitoring studies show that women have been internally exposed to o,p'-DDT at range of 0.3-500 ng/g (8.46×10^{-10} M- 1.41×10^{-6} M) in blood and other tissues. However, very limited studies have investigated the biological effects and mechanism(s) of o,p'-DDT at levels equal to or lower than current exposure levels in human. **In this study, using primary cultures of rat ovarian granulosa cells, we determined that very low doses of o,p'-DDT (10^{-12} - 10^{-8} M) suppressed the expression of ovarian genes and production of prostaglandin E2 (PGE2). In vivo experiments consistently demonstrated that o,p'-DDT at 0.5-1 mg/kg inhibited the gene expression and PGE2 levels in rat ovary.** The surprising results from the receptor inhibitors studies showed that these inhibitory effects were exerted independently of either classical estrogen receptors (ERs) or G protein-coupled receptor 30 (GPR30). Instead, o,p'-DDT altered gene expression or hormone action via inhibiting the activation of protein kinase A (PKA), rather than protein kinase C (PKC). We further revealed that o,p'-DDT directly interfered with the PKA catalytic subunit. Our novel findings support the hypothesis that exposure to low concentrations of o,p'-DDT alters gene expression and hormone synthesis through signaling mediators beyond receptor binding, and imply that the current exposure levels of o,p'-DDT observed in the population likely poses a health risk to female reproduction (Liu, J., M. Zhao et al. 2012).

7.2.4 Respiratory System

Title: DDE in mothers' blood during pregnancy and lower respiratory tract infections in their infants (2010)

ABSTRACT: The association between prenatal levels of DDE and lower respiratory tract infection in infants was studied independently from polychlorinated biphenyls (PCBs) and other organochlorines. **Methods:** Maternal levels of p,p'-DDE, dichlorodiphenyltrichloroethane (p,p'-DDT), PCB congeners 28, 118, 138, 153, and 180, hexachlorobenzene, and β -hexachlorocyclohexane were measured in first trimester serum of 584 pregnant women from a general population-based cohort in Sabadell (Catalonia, Spain). Mothers reported lower respiratory tract infection in interviewer-led questionnaires administered at infant age 6 and 14 months. **Results:** Thirteen percent of babies had recurrent lower respiratory tract infection during the first 14 months of life. Among the organochlorines, DDE showed the highest levels (median = 112 ng/g lipid). The median total PCB level was 85 ng/g. DDE was the only organochlorine that showed an association with recurrent lower respiratory tract infection (at levels >83 ng/g, the first tertile, relative risk = 2.40 [95% confidence interval = 1.19-4.83]), lower respiratory tract infection at 6 months (1.68 [1.06-2.66]), and lower respiratory tract infection at 14 months (1.52 [1.05-2.21]). Adjusting for PCBs, hexachlorobenzene or β -hexachlorocyclohexane did not confound the association. **Conclusions: Immunologic suppression by DDE as observed in experimental studies could explain the relation between DDE and lower respiratory tract infection, independently of PCBs. Exposure to DDE during prenatal life could be critical for the development of the immune and respiratory systems** (Sunyer et al. 2010).

Title: Effects of persistent organic pollutants on the developing respiratory and immune systems: A systematic review (2013)

ABSTRACT: Background: Disruption of developing immune and respiratory systems by early-life exposure to persistent organic pollutants (POPs) could result into reduced capacity to fight infections and increased risk to develop allergic manifestations later in life. Objectives: To systematically review the epidemiologic literature on the adverse effects of early-life exposure to POPs on respiratory health, allergy and the immune system in infancy, childhood and adolescence. Methods: Based on published guidelines for systematic reviews, two independent researchers searched for published articles in MEDLINE and SCOPUS using defined keywords on POPs and respiratory health, immune function and allergy. Study eligibility criteria were defined to select the articles. Results: This review of 41 studies finds limited evidence for prenatal exposure to DDE, PCBs and dioxins and risk of respiratory infections. Evidence was limited also for postnatal exposure to PCBs, specifically ndl-PCBs, and reduced immune response after vaccination in childhood. The review indicates lack of association between postnatal exposure to PCBs/ndl-PCBs and risk of asthma-related symptoms. For the other exposure-outcome associations reviewed evidence was inadequate. Discussion and conclusion: **Current epidemiological evidence suggests that early-life exposure to POPs can adversely influence immune and respiratory systems development. Heterogeneity between studies in exposure and outcome assessment and the small number of studies for any given exposure-outcome relationship currently make comparisons difficult and meta-analyses impossible. Also, mechanisms remain largely unexplored. Recommendations for significantly improving our understanding thus include harmonization of exposure and outcome assessment between studies, conduct of larger studies, long-term assessment of respiratory infections and asthma symptoms in order to identify critical periods of susceptibility, integration of the potential immunotoxic mechanisms of POPs, and use of new statistical tools to detangle the role of multiple exposures on multiple outcomes (Gascon et al. 2013a).**

8. CARCINOGENICITY

8.1 Laboratory animals

8.1.1 Mice

Summary: In conclusion, all nine studies of DDT in eight different mouse strains, including two multigenerational studies, demonstrated some degree of increased tumour incidence caused by DDT. The lowest dose producing increased tumour incidence was approximately 0.26 mg/kg bw per day. Six of these nine studies showed an increase in liver tumours, including two of the three studies with multiple dose groups. Lung tumours were seen in three of the studies in three different strains, but were somewhat inconsistent for BALB/c mice, for which a multigeneration study with low doses demonstrated an increase and an adult exposure higher-dose study did not. Four studies showed increases in leukaemia and/or lymphomas. Both studies using DDE were positive for liver tumours in males and females using two different strains.

Title: Accelerated mammary tumor onset in a HER2/neu mouse model exposed to DDT metabolites locally delivered to the mammary gland (2012)

ABSTRACT: Background: The association of DDT (dichlorodiphenyltrichloroethane) with breast cancer is controversial, but animal studies directly linking DDT to risk are lacking. Concerns with DDT reside in its environmental persistence, bioaccumulation in breast adipose tissue, and endocrine-disrupting actions. Whereas most attention has been focused on

estrogenic congeners, we tested the cancer-inducing potential of the antiandrogen, p,p'-DDE [1,1-dichloro-2,2-bis(p-chlorophenyl) ethylene], the most prevalent and persistent DDT metabolite. Objectives: We aimed to determine whether developmental exposure to p,p'-DDE stored in adipose tissue surrounding the cancer-prone mammary epithelium of MMTV-Neu mice influences tumor development. Methods: For localized delivery, Elvax 40P pellets containing p,p'-DDE were implanted into the mammary fat pads of prepubertal female mice. We compared mammary tumor development with p,p'-DDE with development in response to its estrogenic isomer, o,p'-DDE [1,1-dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl) ethylene], and a mixture of both isomers. Results: p,p'-DDE implants significantly accelerated mammary tumor onset compared with vehicle Elvax implants. o,p'-DDE had similar results, but only at ≤ 10 months of age. Lipid-adjusted levels of p,p'-DDE in mammary adipose tissue and serum in young mice were within the ranges of human exposure, whereas concentrations in aged mice were low to undetectable. Exposure to a 2:1 ratio of p,p'-DDE:o,p'-DDE did not result in the younger latency observed with the individual isomers. Conclusions: p,p'-DDE exposure at concentrations relevant to human exposure accelerates mammary carcinogenesis in mice, possibly through hormonal and/or other actions. **These data suggest that DDE exposure would promote, but not cause, mammary tumorigenesis. Developmental exposure in immature mammary tissue continues to affect tumor onset even after p,p'-DDE levels have declined. Future studies are needed to determine whether early exposure to p,p'-DDE correspondingly predisposes women to early-onset breast cancer** (Johnson et al. 2012).

Title: Dichlorodiphenyltrichloroethane technical mixture regulates cell cycle and apoptosis genes through the activation of CAR and ER α in mouse livers (2013)

ABSTRACT: Dichlorodiphenyltrichloroethane (DDT) is a widely used organochlorine pesticide and a xenoestrogen that promotes rodent hepatomegaly and tumours. A recent study has shown significant correlation between DDT serum concentration and liver cancer incidence in humans, but the underlying mechanisms remain elusive. We hypothesised that a mixture of DDT isomers could exert effects on the liver through pathways instead of classical ERs. The acute effects of a DDT mixture containing the two major isomers p,p'-DDT (85%) and o,p'-DDT (15%) on CAR and ER α receptors and their cell cycle and apoptosis target genes were studied in mouse livers. ChIP results demonstrated increased CAR and ER α recruitment to their specific target gene binding sites in response to the DDT mixture. The results of real-time RT-PCR were consistent with the ChIP data and demonstrated that the DDT was able to activate both CAR and ER α in mouse livers, leading to target gene transcriptional increases including Cyp2b10, Gadd45 β , cMyc, Mdm2, Ccnd1, cFos and E2f1. Western blot analysis demonstrated increases in cell cycle progression proteins cMyc, Cyclin D1, CDK4 and E2f1 and anti-apoptosis proteins Mdm2 and Gadd45 β . In addition, DDT exposure led to Rb phosphorylation. Increases in cell cycle progression and anti-apoptosis proteins were accompanied by a decrease in p53 content and its transcriptional activity. However, the DDT was unable to stimulate the β -catenin signalling pathway, which can play an important role in hepatocyte proliferation. **Thus, our results indicate that DDT treatment may result in cell cycle progression and apoptosis inhibition through CAR- and ER α -mediated gene activation in mouse livers. These findings suggest that the proliferative and anti-apoptotic conditions induced by CAR and ER α activation may be important contributors to the early stages of hepatocarcinogenesis as produced by DDT in rodent livers** (Kazantseva, Yarushkin and Pustyl'niak 2013).

8.1.1.2 Rats

Summary: In conclusion, three of the four studies using three different strains of rats showed an increase in liver tumours. One of these studies had positive effects only in females, and another was negative when repeated by NCI using similar doses (but with shorter duration), the same strain, larger sample sizes, better reporting and complete histopathology. One study also showed an increase in thyroid tumours in males, but statistical significance was not in thyroid follicular cell adenomas and carcinomas in female rats at the low dose, but not at the high dose, and another had a suggestion of a trend in thyroid tumours in males, but statistical significance was not assessed. The one study of DDE in rats was negative.

8.1.1.2.1 Long term, non-carcinogenic effects in rats

Title: *p,p'-DDT induces microcytic anemia in rats (2013)*

Emerging evidence suggests that chronic exposure to DDT and its derivatives is associated with a variety of human disorders such as anemia. The present study demonstrated that *p,p'*-DDT caused microcytic anemia in a dose-dependent manner (0, 5, 50, and 500 ppm) in the long-term study up to 2 years. To elucidate the mechanism(s) by which *p,p'*-DDT induces anemia, certain hematological parameters were assessed in rats fed specific doses of *p,p'*-DDT for 2 weeks, and the effect of lipopolysaccharide on anemia of inflammation was also examined in *p,p'*-DDT-treated rats. The parameters included the content of hemoglobin per reticulocyte, mean corpuscular volume of reticulocytes and mature erythrocytes, corpuscular hemoglobin concentration mean of mature erythrocytes, and saturation levels of transferrin and iron. During the 2-week treatment period, hypochromic microcytic reticulocytes and hypochromic normocytic mature erythrocytes were observed in *p,p'*-DDT-treated rats, with no evidence of alteration in plasma iron levels. *p,p'*-DDT enhanced microcytosis of reticulocytes, as well as mature erythrocytes, which occurred due to severe hypoferremia resulting from anemia of inflammation; however, plasma iron levels were attenuated probably through the inhibition of interleukin-6. **Our data suggests that long-term treatment with *p,p'*-DDT induces microcytic anemia, possibly because of the impairment of iron utility in erythrocytes** (Tomita et al. 2013).

8.1.1.3 Other laboratory animals

Summary: Studies in other test species (dogs and monkeys) have been too small and/or short term to be conclusive. A short-term study on testicular cancer after perinatal exposure in rabbits was inconclusive.

8.1.1.4 Human cell lines

Title: *In vitro combined cytotoxic effects of pesticide cocktails simultaneously found in the French diet (2013)*

ABSTRACT: Although human populations may be constantly exposed to complex pesticide mixtures through their diet, the human health risk of pesticide exposure is currently assessed on the basis of toxicity data on individual compounds. To investigate the combined toxic effects of pesticide cocktails previously identified in the French diet, we first studied the cytotoxicity induced by seven cocktails composed of two to six pesticides on human hepatic (HepG2) and colon (Caco-2) cell lines using the MTT and neutral red uptake assays. Secondly, we challenged to assess the combined effects of the two most cytotoxic cocktails by

comparing the measured effects of the mixtures with the predictions based on additive effects on two concepts-independent action (IA) and concentration addition (CA). For the cocktail composed of dichlorodiphenyltrichloroethane (DDT) and dieldrin, the cytotoxicity of the equimolar cocktail proved greater than the additive effect estimated by the two concepts. Furthermore, apoptosis induction was higher in equimolar cocktail than predicted by summing the effects of DDT and dieldrin. **Thus, some supra-additive toxicity was found in the DDT-dieldrin cocktail. Nevertheless, if IA and CA models could reveal combined effects of pesticide cocktails, an accurate evaluation remains challenging** (Takakura et al. 2013).

8.1.4 Conclusions for laboratory animals

8.2 Humans

8.2.1 Ecological and cohort studies

Summary: Ecological and cohort studies for DDT do not provide convincing evidence of patterns of associations between DDT and cancer incidence or mortality. However, these studies all have severe limitations. Most, except for Austin et al. (1989), lack individual DDT or DDE exposure measures and instead rely on occupational history, self-report or ecological measures of exposure, which are likely to be unreliable. Some, such as Austin et al. (1989), are too small to have adequate statistical power to observe an increased incidence of cancer associated with DDT. Of the others, all but Purdue et al. (2007) examine cancer mortality but not cancer incidence. Also, most of those studies did not include patho-logical confirmation of cancer case status.

8.2.2 Case-control and nested case-control studies

8.2.2.1 Breast cancer

Summary: For breast cancer epidemiological studies, exposures to DDT and DDE as ascertained at the time of diagnosis or during adulthood are generally not associated with breast cancer; there are some positive studies, but they are outweighed by an overwhelming number of negative studies, as is clear from the López-Cervantes et al. (2004) meta-analysis and a number of the studies completed since that time. Most of the ecological and cohort studies (Table 3) included males only; one (Cocco et al., 2000) did not support a relationship between DDT and breast cancer. A single study of prepubertal exposure to DDT suggested that early life (prior to age 14) exposure, but not later, may be associated with breast cancer.

Title: Assessment of exposure to persistent organochlorine compounds in epidemiological studies on breast cancer: A literature review and perspectives for the Cecile study (2010)

ABSTRACT: Breast cancer is the most frequent neoplastic disease in women representing 50,000 new cases each year in France. The well-established risk factors, as those related to the reproductive history, cannot account for all cases of breast cancer. Other environmental or lifestyle factors need to be explored in depth. Persistent organochlorine compounds (OCs) have attracted attention because of their endocrine disrupting properties that make them possible risk factors for breast cancer, but most epidemiological studies did not report an association between OC concentrations in blood or adipose tissue and breast cancer risk. In these studies, OC levels were measured in biological samples obtained at the time of cancer diagnosis or only a few years before.

In this paper, we review the studies on dichlorodiphenyltrichloroethane (DDT) and polychlorobiphenyl (PCB) exposures in relation to breast cancer. We discuss the relevance of OC biological measurements as lifelong exposure indicators, and we describe a new method for assessing exposure to OCs in epidemiological studies. Most studies were carried out recently and reported OC concentrations that were substantially lower than those reported during the 1960s and 1970s. We make the assumption that these OC levels were not reliable

indicators, as they were not measured during etiologically relevant periods in a woman's lifetime, i.e. during the prenatal period, the puberty or the period before a first full-term pregnancy, which are regarded as key periods of vulnerability of mammary gland cells to carcinogens. This may have resulted in non differential exposure misclassification and hence in the absence of an observed association between OC levels and breast cancer in most epidemiological studies. Physiologically-based pharmacokinetic (PBPK) models allow estimating persistent organic pollutant lifetime toxicokinetics profiles retrospectively in women, by taking into account individual differences in metabolism and key events that affect OC kinetics such as lactation and weight variations. PBPK models will be applied to the participants of a large French population-based case-control study including 1080 cases and 1055 controls. Exposure misclassification could have prevented from observing an association between exposure to OCs and breast cancer risk. **PBPK models could be used as a novel way of assessing exposure to OCs and to investigate the impact of internal exposure at different time windows on breast cancer incidence (Bachelet et al. 2010).**

Title: Accumulation of environmental estrogens in adipose tissue of breast cancer patients (2010)

Although the estrogenic properties of numerous chloroorganic pesticides have been widely recognized, population studies do not give clear results indicating the link between the exposure to these compounds and breast cancer development. Because of the weak affinity of these pesticides to estrogen receptors, they probably act by affecting the expression of CYP genes encoding cytochromes P450 engaged in the metabolism of environmental as well as natural estrogens. To examine the possible correlation between environmental estrogen levels in adipose tissue and breast cancer stage, grade, receptor status and onset of the disease, adipose tissue was isolated from 54 breast cancer patients and 23 healthy individuals. Clinical characteristics were obtained from the medical records, while the information concerning exposure to environmental estrogens were obtained from questionnaires. The environmental estrogens were identified and quantified by GC-chromatography. The data was analyzed with the use of Student t-test and Spearman correlation. The levels of most environmental estrogens did not differ between the patients and the controls, except the β -HCH (β -hexachlorocyclohexane) level, which was higher in the patients than in the healthy individuals. Significantly higher levels of DDE (1,1-bis(4-chlorophenyl)-2,2-dichloroethene) and DDT (1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane) ($P < 0.05$) were observed in the patients with late onset of the disease which was probably due to the time of exposure. Moreover, in the patients exposed to environmental estrogens, significantly higher concentrations of DDD (1,1-bis(4-chlorophenyl)-2,2-dichloroethane) were found ($P < 0.05$). We also evidenced that estrogen-independent cancer was more frequent in the patients exposed to numerous risk factors in which higher levels of HCB (hexachlorobenzene), γ -HCH (γ -hexachlorocyclohexane), DDD and DDT in adipose tissue were detected. **Breast cancer development is probably related to the accumulation of DDT and its derivatives, but the effect appears only in older patients. We postulate that environmental estrogens acting together with other risk factors might influence the progress and exacerbate the prognosis of breast cancer (Ociepa-Zawal et al. 2010).**

Title: Environmental causes of breast cancer and radiation from medical imaging: Findings from the Institute of Medicine report (2012)

ABSTRACT: Susan G. Komen for the Cure asked the Institute of Medicine (IOM) to perform a comprehensive review of environmental causes and risk factors for breast cancer.

Interestingly, none of the consumer products (ie, bisphenol A, phthalates), industrial chemicals (ie, benzene, ethylene oxide), or pesticides (ie, DDT/DDE) considered could be conclusively linked to an increased risk of breast cancer, although the IOM acknowledged that the available evidence was insufficient to draw firm conclusions for many of these exposures, calling for more research in these areas. The IOM found sufficient evidence to conclude that the 2 environmental factors most strongly associated with breast cancer were exposure to ionizing radiation and to combined postmenopausal hormone therapy. The IOM's conclusion of a causal relation between radiation exposure and cancer is consistent with a large and varied literature showing that exposure to radiation in the same range as used for computed tomography will increase the risk of cancer. It is the responsibility of individual health care providers who order medical imaging to understand and weigh the risk of any medical procedures against the expected benefit (Smith-Bindman 2012).

Title: Complex organochlorine pesticide mixtures as determinant factor for breast cancer risk: A population-based case-control study in the Canary Islands (Spain) (2012)

Abstract: Background: All the relevant risk factors contributing to breast cancer etiology are not fully known. Exposure to organochlorine pesticides has been linked to an increased incidence of the disease, although not all data have been consistent. Most published studies evaluated the exposure to organochlorines individually, ignoring the potential effects exerted by the mixtures of chemicals. Methods: This population-based study was designed to evaluate the profile of mixtures of organochlorines detected in 103 healthy women and 121 women diagnosed with breast cancer from Gran Canaria Island, and the relation between the exposure to these compounds and breast cancer risk. Results: The most prevalent mixture of organochlorines among healthy women was the combination of lindane and endrin, and this mixture was not detected in any affected women. Breast cancer patients presented more frequently a combination of aldrin, dichlorodiphenyldichloroethylene (DDE) and dichlorodiphenyldichloroethane (DDD), and this mixture was not found in any healthy woman. **After adjusting for covariables, the risk of breast cancer was moderately associated with DDD (OR = 1.008, confidence interval 95% 1.001-1.015, p = 0.024).** **Conclusions: This study indicates that healthy women show a very different profile of organochlorine pesticide mixtures than breast cancer patients, suggesting that organochlorine pesticide mixtures could play a relevant role in breast cancer risk** (Boada, L. D., Zumbado M. et al. 2012)

Title: Effects of environmental organochlorine pesticides on human breast cancer: Putative involvement on invasive cell ability (2013)

ABSTRACT: Human exposure to persistent organic pollutants (POPs) is a certainty, even to long banned pesticides like o,p'-dichlorodiphenyltrichloroethane (o,p'-DDT), and its metabolites p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE), and p,p'-dichlorodiphenyldichloroethane (p,p'-DDD). POPs are known to be particularly toxic and

have been associated with endocrine-disrupting effects in several mammals, including humans even at very low doses. As environmental estrogens, they could play a critical role in carcinogenesis, such as in breast cancer. With the purpose of evaluating their effect on breast cancer biology, o,p'-DDT, p,p'-DDE, and p,p'-DDD (50-1000 nM) were tested on two human breast adenocarcinoma cell lines: MCF-7 expressing estrogen receptor (ER) α and MDA-MB-231 negative for ER α , regarding cell proliferation and viability in addition to their invasive potential. Cell proliferation and viability were not equally affected by these compounds. In MCF-7 cells, the compounds were able to decrease cell proliferation and viability. On the other hand, no evident response was observed in treated MDA-MB-231 cells. Concerning the invasive potential, the less invasive cell line, MCF-7, had its invasion potential significantly induced, while the more invasive cell line MDA-MB-231, had its invasion potential dramatically reduced in the presence of the tested compounds. Altogether, the results showed that these compounds were able to modulate several cancer-related processes, namely in breast cancer cell lines, and underline the relevance of POP exposure to the risk of cancer development and progression, unraveling distinct pathways of action of these compounds on tumor cell biology (Pestana et al. 2013).

Title: DDT/DDE and breast cancer: A meta-analysis (2013)

The biological basis for investigating dichlorodiphenyltrichloroethane (DDT) exposure and breast cancer risk stems from in vitro and animal studies indicating that DDT has estrogenic properties. The objective of this study was to update a meta-analysis from 2004 which found no association between dichlorodiphenyldichloroethylene (DDE) and breast cancer. We searched PubMed and Web of Science for studies published through June 2012 assessing DDT/DDE exposure and breast cancer. Summary Odds Ratios (ORs) with 95% confidence intervals (CIs) were calculated for the prevalence of breast cancer in the highest versus the lowest exposed groups for DDT and DDE. Difference of means of exposure for cases versus controls was analyzed for DDT and DDE. From the 500 studies screened, 46 were included in the meta-analysis. Slightly elevated, but not statistically significant summary ORs were found for DDE (1.05; 95% CI: 0.93-1.18) and DDT (1.02; 95% CI: 0.92-1.13). Lipid adjusted difference of means analysis found a significantly higher DDE concentration in cases versus controls (11.30. ng/g lipid; p= 0.01). No other difference of means analysis found significant relationships. **The existing information does not support the hypothesis that exposure to DDT/DDE increases the risk of breast cancer in humans** (Ingber et al. 2013).

8.2.2.2 Testicular cancer

Summary: For testicular cancer epidemiological studies, a single study with a prospective exposure measure provided evidence for an association between DDE exposure and testicular germ cell tumours at levels above 0.39 μ g/g lipid.

Title: Pesticide exposure and serum organochlorine residuals among testicular cancer patients and healthy controls (2011).

ABSTRACT: The incidence of testicular cancer (TC) has been increasing worldwide during the last decades. The reasons of the increase remains unknown, but recent findings suggest that organochlorine pesticides (OPs) could influence the development of TC. A hospital-based

case-control study of 50 cases and 48 controls was conducted to determine whether environmental exposure to OPs is associated with the risk of TC, and by measuring serum concentrations of OPs, including p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE) isomer and hexachlorobenzene (HCB) in participants. A significant association was observed between TC and household insecticide use (odds ratio [OR] = 3.01, 95 % CI: 1.11-8.14; OR(adjusted) = 3.23, 95 % CI: 1.15-9.11). Crude and adjusted ORs for TC were also significantly associated with higher serum concentrations of total OPs (OR = 3.15, 95 % CI: 1.00-9.91; OR(adjusted) = 3.34, 95 % CI: 1.09-10.17) in cases compared with controls. **These findings give additional support to the results of previous research that suggest that some environmental exposures to OPs may be implicated in the pathogenesis of TC** (Giannandrea et al 2011).

Title: Organochlorine compounds and testicular dysgenesis syndrome: Human data (2011)

ABSTRACT: Cryptorchidism, hypospadias, subfertility and testicular germ-cell tumour have been suggested to comprise a testicular dysgenesis syndrome (TDS) based on the premise that each may derive from perturbations of embryonal programming and gonadal development during foetal life. Endocrine-disrupting chemicals have been hypothesized to be associated with these disorders, given the importance of sex steroid hormones in urogenital development and homeostasis. Organochlorines are one such set of compounds which are defined as containing between one and ten covalently bonded chlorine atoms. These compounds are persistent pollutants with long half-lives, accumulate in adipose tissue when ingested, bioaccumulate and biomagnify, and have complex and variable toxicological profiles. Examples of organochlorines include dichloro-diphenyl-trichloroethane and its metabolites, polychlorinated biphenyls, and chlordane. In this comprehensive review of human epidemiologic studies which have tested for associations between organochlorines and facets of TDS, **we find evidence for associations between the exposures p,p'-DDE, cis-nonachlor and trans-nonachlor with testicular germ-cell tumour.** The sum of the evidence from human epidemiological studies does not indicate any association between specific organochlorines studied and cryptorchidism, hypospadias or fertility. Many other endocrine-disrupting chemicals, including additional organochlorines, have yet to be assessed in relation to disorders associated with TDS, yet study of such chemicals has strong scientific merit given the relevance of such hypotheses to urogenital development (Cook et al. 2011).

8.2.2.3 Liver cancer

<p>Summary: A single incidence study provides strong evidence for an association between DDT (geometric mean 0.49 µg/g) but not DDE (geometric mean 2.9 µg/g in cases, 3.0 µg/g in controls) levels in serum and liver cancer among relatively highly exposed populations. Other studies have not been positive, but this is the only study with individual prospective measures of DDT exposure and complete ascertainment of cancer incidence.</p>

Title: Exposure to organochlorine pesticides is independent risk factor of hepatocellular carcinoma: A case-control study

ABSTRACT: Zhao et al. (2011) investigated, if organochlorine pesticides (OCPs) exposure contributed to primary hepatocellular carcinoma (HCC) risk in the Xiamen population of China.

The questionnaire database was built from 346 HCC cases and 961 healthy controls during 2007-2009. The serum levels of α -, β -, γ -, δ -HCH, p, p'-DDT, p, p'-DDE, o, p'-DDT and p, p'-DDD were measured by gas chromatography-tandem mass spectrometer and statistical analysis was done using SPSS16. P, p'-DDT, p, p'-DDE, displayed quartile dose-dependent HCC risk trends; p, p'-DDT showed positive (i.e., synergistic) interactions with HBV, diabetes mellitus, AFB1 and polycyclic aromatic hydrocarbon (PAH) exposure, but negative (i.e., antagonistic) interaction with heavy drinking; p, p'-DDE had positive interaction with PAH but negative interaction with HBV and p, p'-DDT; and β -HCH was positively interacted with p, p'-DDT but negatively interacted with heavy drinking and diabetes. **p, p'-DDT, p, p'-DDE and β -HCH were independent HCC risk factors. Because of their synergistic interactions with other factors, the high level exposure combined with common AFB1 and HBV exposure in the investigated area may greatly enhance the risk of HCC.**

Title: Dichlorodiphenyltrichloroethane and risk of hepatocellular carcinoma (2012)

ABSTRACT: Dichlorodiphenyltrichloroethane (p,p'-DDT), an organochlorine pesticide known to have deleterious health effects in humans, has been linked to hepatocellular carcinoma (HCC) in rodents. A recent study has reported that p,p'-DDT and its most persistent metabolite, dichlorodiphenyldichloroethylene (p,p'-DDE), may also be associated with HCC in humans. To examine whether there is an association between p,p'-DDT and/or p,p'-DDE in a population at high-risk of developing HCC, a nested case-control study was conducted within the 83,794 person Haimen City Cohort in China. Sera and questionnaire data were collected from all participants between 1992 and 1993. This study included 473 persons who developed HCC and 492 who did not, frequency matched on sex, age and area of residence. p,p'-DDT and p,p'-DDE levels were determined by mass spectrometry. Hepatitis B viral infection status (based on hepatitis B virus surface antigen; HBsAg) was also determined. p,p'-DDT and/or p,p'-DDE serum levels were significantly associated with sex, area of residence, occupation, alcohol consumption and cigarette smoking. Adjusting for age, sex, area of residence, HBsAg, family history of HCC, history of acute hepatitis, smoking, alcohol, occupation (farmer vs. other) and levels of p,p'-DDT or p,p'-DDE, odds ratios (OR) and 95% confidence intervals (CI) were calculated via unconditional logistic regression. **Overall, the highest quintile of p,p'-DDT was associated with an increased risk of HCC, OR = 2.96 95% CI; 1.19-7.40. There were no statistically significant associations with p,p'-DDE. Overall, these results suggest that recent exposure to p,p'-DDT may increase risk of HCC (Persson et al 2012).**

8.2.2.4 Lymphocytic cancers

Summary: Cohort and ecological studies did not find relationships between DDT and lymphocytic cancers (Table 3). Most studies linking pesticide exposure to NHL did not distinguish DDT from other chemicals as the causative agent. A single case-control study that adjusted for other pesticide exposures did not show a significant association with DDT exposure.

Title: Increased risk of non-Hodgkin lymphoma and serum organochlorine concentrations among neighbors of a municipal solid waste incinerator (2011)

ABSTRACT: Organochlorine chemicals may contribute to an increased risk of non-Hodgkin lymphoma (NHL) within non-occupationally exposed populations. Among these chemicals,

dioxins and furans were mainly released by municipal solid waste incinerators (MSWIs) until a recent past in France, a source of exposure that is of public concern. We investigated organochlorines and the risk of NHL among neighbors of a French MSWI with high levels of dioxin emissions (Besançon, France), using serum concentrations to assess exposure. The study area consisted of three electoral wards, containing or surrounding the MSWI. Pesticides, dioxins, furans, and polychlorinated biphenyls (PCBs) were measured in the serum of 34 newly diagnosed NHL cases (2003-2005) and 34 controls. Risks of NHL associated with each lipid-corrected serum concentration were estimated using exact logistic regression. The pesticides β -hexachlorocyclohexane (odds ratio [OR]=1.05, 95% confidence interval [CI]=1.00-1.12, per 10ng/g lipid) and p,p' dichloro-diphenyl-trichloroethane (DDT) (OR=1.20, 95% CI=1.01-1.45, per 10ng/g lipid) were associated with NHL risk. Evidence indicated an increased NHL risk associated with cumulative WHO 1998-toxic equivalency factor (TEQ) concentrations (dioxins, OR=1.12, 95% CI=1.03-1.26; furans, OR=1.16, 95% CI=1.03-1.35; dioxin-like PCBs, OR=1.04, 95% CI=1.00-1.07; and total TEQ, OR=1.04, 95% CI=1.01-1.05), as well as with non dioxin-like PCBs (OR=1.02, 95% CI=1.01-1.05, per 10ng/g lipid). Most congener-specific associations were statistically significant. **This study provides strong and consistent support for an association between serum cumulative WHO 1998-TEQ concentrations, at levels experienced by people residing in the vicinity of a polluting MSWI, and risk of NH (Viel et al. 2011).**

Title: A prospective study of organochlorines in adipose tissue and risk of non-Hodgkin lymphoma (2012)

ABSTRACT: Background: Exposure to organochlorines has been examined as a potential risk factor for non-Hodgkin lymphoma (NHL), with inconsistent results that may be related to limited statistical power or to imprecise exposure measurements. Objective: Our purpose was to examine associations between organochlorine concentrations in prediagnostic adipose tissue samples and the risk of NHL. Methods: We conducted a case-cohort study using a prospective Danish cohort of 57,053 persons enrolled between 1993 and 1997. Within the cohort we identified 256 persons diagnosed with NHL in the population-based nationwide Danish Cancer Registry and randomly selected 256 subcohort persons. We measured concentrations of 8 pesticides and 10 polychlorinated biphenyl (PCB) congeners in adipose tissue collected upon enrollment. Associations between the 18 organochlorines and NHL were analyzed in Cox regression models, adjusting for body mass index. Results: Incidence rate ratios and confidence intervals (CIs) for interquartile range increases in concentrations of dichlorodiphenyltrichlorethane (DDT), cis-nonachlor, and oxychlordane were 1.35 (95% CI: 1.10, 1.66), 1.13 (95% CI: 0.94, 1.36), and 1.11 (95% CI: 0.89, 1.38), respectively, with monotonic dose-response trends for DDT and cis-nonachlor based on categorical models. The relative risk estimates were higher for men than for women. In contrast, no clear association was found between NHL and PCBs. **Conclusion: We found a higher risk of NHL in association with higher adipose tissue levels of DDT, cis-nonachlor, and oxychlordane, but no association with PCBs. This is the first study of organochlorines and NHL using prediagnostic adipose tissue samples in the exposure assessment and provides new environmental health evidence that these organochlorines contribute to NHL risk (Bräuner et al. 2012) (01)**

8.2.2.5 Lung cancer

Summary: Data are inadequate to assess any possible associations between DDT/DDE and lung cancer.

8.2.2.6 Pancreatic cancer

Summary: Studies linking pesticide exposure to pancreatic cancer generally did not distinguish DDT from other chemicals as the causative agent. One small study indicates a possible association between both DDT and DDE and a subtype of pancreatic cancer with a specific *K-ras* mutation. In conclusion, data are inadequate to assess associations between DDT/DDE and pancreatic cancer.

8.2.2.7 Other cancer (Prostate, Endometrial)

Summary: Data are insufficient to assess any possible association between DDT/DDE exposures and either prostate or endometrial cancer.

Title: Prostate cancer risk and exposure to pesticides in British Columbia Farmers (2011)

ABSTRACT: As published by Band et al. (2011), several epidemiologic studies have reported an increased risk of prostate cancer among farmers.

To assess the risk of developing prostate cancer in relation to exposure, a case-control approach was used with 1,516 prostate cancer patients and 4,994 age-matched internal controls consisting of all other cancer sites excluding lung cancer and cancers of unknown primary site. Lifetime occupational history was obtained through a self-administered questionnaire and used in conjunction with a job exposure matrix to estimate the participants' lifetime cumulative exposure to approximately 180 active compounds in pesticides.

Conditional logistic regression was used to assess prostate cancer risk, adjusting for potential confounding variables and effect modifiers. These include age, ethnicity, alcohol consumption, smoking, education, and proxy respondent.

There was a significant association between prostate cancer risk and exposure to DDT (OR=1.68; 95% CI: 1.04-2.70 for high exposure) which is in keeping with those previously reported in the literature.

Title: Plasma organochlorine levels and prostate cancer risk (2010)

ABSTRACT: A case-control study was conducted to determine the association between plasma organochlorine levels and prostate cancer risk. Male clinic patients scheduled for prostate core biopsy or seeing their urologist for other conditions from 1997 through 1999 in Kingston, Ontario were eligible, excluding those with an earlier cancer. Age frequency matched controls (n=329) were compared with 79 incident prostate cancer cases. Before knowledge of diagnosis, the patients completed a questionnaire and donated 15 ml of blood for the measurement of 14 PCBs, and 13 organochlorine pesticides by gas chromatography. At least 70% of patients had detectable levels of nine PCB congeners and seven pesticides, and these chemicals were included in the risk analysis adjusted for total lipids. Geometric means for these PCB congeners, total PCBs, and p,p'-DDE are slightly lower for cases than controls, whereas the levels of p,p'-DDT and other pesticides are virtually equal. Adjusting for age and other confounders in multivariable logistic regression, odds ratios (ORs) are consistently below 1.0 for PCB congeners and total PCBs. For pesticides, most ORs are very close to the null. **This study suggests that long-term low-level exposure to organochlorine pesticides and PCBs in the general population does not contribute to increased prostate cancer risk (Aronson et al, 2010.).**

Title: Plasma organochlorines and subsequent risk of prostate cancer in Japanese men (2010)

ABSTRACT: Although accumulating evidence suggests that exposure to organochlorine pesticides and polychlorinated biphenyls (PCBs) may contribute to the development of prostate cancer, few investigations have used biological samples to classify exposure to specific organochlorines. To our knowledge, this is the first prospective study to investigate the association between blood levels of organochlorines and prostate cancer risk. **Methods:** We conducted a nested case-control study using data from the Japan Public Health Center-based Prospective (JPHC) Study. A total of 14,203 men 40-69 years old who returned the baseline questionnaire and who provided blood samples were followed from 1990 to 2005. Using a mean follow-up period of 12.8 years, we identified 201 participants who were newly diagnosed with prostate cancer. Two matched controls for each case were selected from the cohort. We used a conditional logistic regression model to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for prostate cancer in relation to plasma levels of nine organochlorines: PCBs, dichlorodiphenyltrichloroethane (DDT), hexachlorobenzene (HCB), β -hexachlorocyclohexane (β -HCH), trans- and cis-nonachlor, oxychlordane, and mirex. **Results:** No statistically significant association with total prostate cancer was seen for any plasma organochlorine, although we did observe an insignificant inverse association for plasma HCB and β -HCH. Total PCB in plasma was also inversely associated with advanced prostate cancer but without statistical significance. **Conclusion:** **Our results suggest that no overall association exists between prostate cancer and organochlorines at the levels measured in our study population** (Sawada et al. 2010).

8.3 Mode of action

Summary: DDT causes cancer in several species of animals and in several organ systems. There are likely multiple modes of action for tumour induction that may be operational simultaneously, particularly when chronic exposures are involved. Because many of the mechanistic studies were not conducted under conditions of the bioassays, the form of the dose-response curve cannot be well defined at the molecular level. DDT is known to bind to CAR, which may mediate the hepatocarcinogenic effects observed in rodents. In initiation and promotion studies, DDT is a promoter of rat liver foci. Disruption of cellular communication would be expected to promote progression of cancer development. Finally, although DDT and DDE have not generally been considered to be genotoxic, there is evidence, particularly in human and mammalian systems, for DNA damage (and apoptosis) in lymphocytes with higher level exposures. The possibility that such exposures, even transiently, are involved with carcinogenesis cannot be dismissed. Endocrine disruption per se can be a mechanism for carcinogenicity of endocrine organs, either by promoting growth of hormone receptor-positive tumours or via epigenetic mechanisms. No mode of action has been proposed for DDT carcinogenicity that is specific to animals and would not be relevant to humans (see IPCS, 2007).

Title: Effects of DDT and triclosan on tumor-cell binding capacity and cell-surface protein expression of human natural killer cells (2013)

ABSTRACT: 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT) and triclosan (TCS) are organochlorine (OC) compounds that contaminate the environment, are found in human blood and have been shown to decrease the tumor-cell killing (lytic) function of human natural killer (NK) cells. NK cells defend against tumor cells and virally infected cells. They bind to these targets, utilizing a variety of cell surface proteins. The present study examined concentrations of DDT and TCS that decrease lytic function for alteration of NK binding to tumor targets. Levels of either compound that caused loss of binding function were then examined for effects on expression of cell-surface proteins needed for binding. NK cells exposed to 2.5 μ M

DDT for 24 h (which caused a greater than 55% loss of lytic function) showed a decrease in NK binding function of about 22%, and a decrease in CD16 cell-surface protein of 20%. NK cells exposed to 5 µM TCS for 24 h showed a decrease in ability to bind tumor cells of 37% and a decrease in expression of CD56 of about 34%. This same treatment caused a decrease in lytic function of greater than 87%. **These results indicated that only a portion of the loss of NK lytic function seen with exposures to these compounds could be accounted for by loss of binding function. They also showed that loss of binding function is accompanied by a loss of cell-surface proteins important in binding function** (Hurd-Brown et al. 2013).

9. GENOTOXICITY

9.1 Summary of past studies

Dozens of genotoxicity studies with DDT and its metabolites have been summarized by IARC (1991) and ATSDR (2002). Based on data available in 1990, IARC concluded that whereas conflicting data were obtained with regard to some genetic end-points, in most studies, DDT did not induce genotoxic effects in rodent or human cell systems, nor was it mutagenic to fungi or bacteria.

9.2 Recent studies 88

Summary: DDT is inactive in most genetic toxicity assays, although it has been shown in some studies to induce DNA damage in human lymphocytes, both in vitro and in bio-monitoring studies, and in cultured rodent cells. These data do not allow discrimination between primary and secondary genotoxic effects. There is also a lack of consistency between findings from experimental animal and in vitro studies.

9.2.1 Laboratory animals and in vitro systems

Title: Genotoxic effect of chronic exposure to DDT on lymphocytes, oral mucosa and breast cells of female rats (2011)

ABSTRACT: Canales-Aguirre et al. (2011) evaluated the genotoxic potential of DDT on systemic and mammary gland cells obtained from adult female Wistar rats. Oral mucosa cells micronuclei were assessed; the comet assay in peripheral blood-isolated lymphocytes and mammary epithelial cells was also carried out. Additionally, oxidative stress was studied in mammary tissue through a lipid peroxidation assay. The data showed an increase in lipid peroxidation, product of an increase in free oxygen radical levels, which leads to an oxidative stress status. **The results suggest that DDT is genotoxic, not only for lymphocytes but also to mammary epithelial cells.**

9.2.2 Humans

Title: DNA damage induced by trans, trans-2,4-decadienal (tt-DDE), a component of cooking oil fume, in human bronchial epithelial cells (2010)

ABSTRACT: Epidemiological studies have demonstrated that cooking oil fumes (COF) are an environmental risk factor for the development of lung adenocarcinoma among nonsmoking females in Taiwan. Aside from polycyclic aromatic hydrocarbons, aldehydes, especially trans, trans-2,4-decadienal (tt-DDE) are found to be abundant in COF. Although there is indication

that tt-DDE induces DNA damage, the precise role of tt-DDE in the induction of DNA damage in lung cells is still not clear. When we assessed DNA breaks with the Comet assay, we found that the DNA breaks induced by 1 μ M tt-DDE in human bronchial epithelial cells (BEAS-2B) could be significantly reduced by antioxidants, suggesting that oxidative stress was involved. Indeed, when tt-DDE-treated cells were coincubated with endonuclease III/formamidopyrimidine-DNA glycosylase or with nuclear extract (NE), an enhancement of DNA breaks was observed at 1 hr after tt-DDE exposure. Furthermore, when NE was incubated with an antibody against 8-oxoguanine DNA glycosylase (anti-OGG1), a reduction in tt-DDE/NE-induced DNA breaks could be demonstrated. Since OGG1 is a specific repair enzyme for 8-oxodeoxyguanosine (8-oxo-dG), these findings indicated that 8-oxo-dG was involved. On the other hand, when NE was incubated with antibodies against nucleotide excision repair enzymes, there was a significant reduction in tt-DDE/NE-induced DNA breaks at 4 hr after tt-DDE treatment. These observations indicate that, in addition to early oxidative DNA damage, nonoxidative DNA damage such as bulky adduct formation, was also induced by tt-DDE. **Our study further affirms that tt-DDE is genotoxic to human lung cells and can increase carcinogenic risk** (Young et al. 2010).

Title: Cytogenetic status of human lymphocytes after exposure to low concentrations of p,p'-DDT, and its metabolites (p,p'-DDE, and p,p'-DDD) in vitro (2012)

ABSTRACT: Despite that the use of DDT has been restricted for more than 40 years to malaria affected areas, low doses of this pesticide and its metabolites DDE and DDD can be found in the environment around the world. Although it has been shown that these pollutants induce cell and DNA damage, the mechanisms of their cytogenotoxic activity remains largely unknown. This study looks into their possible genotoxic effects, at doses that can be found in body fluids, on human lymphocytes using the cytokinesis-block micronucleus assay and the comet assay. After exposure for 1, 6, and 24h compounds p,p'-DDT (0.1 μ g/mL⁻¹), p,p'-DDE (4.1 μ g/mL⁻¹), and p,p'-DDD (3.9 μ g/mL⁻¹) showed increase in DNA damage. The most significant results were observed at exposure period of 24h where number of micronucleated cells increased from control 2.5 \pm 0.71 to 23.5 \pm 3.54, 13.5 \pm 0.71, and 16.5 \pm 6.36 for DDT, DDE, and DDD, respectively. Similar effect was observed using comet test where the percentage of DNA in comets tail increased from control 1.81 \pm 0.16 to 17.24 \pm 0.55, 11.21 \pm 0.56 and 9.28 \pm 0.50 for each compound, respectively. At the same time Fpg-comet assay failed to report induction of oxidative DNA damage of these pollutants. Additionally, the type of cell death was determined using diffusion assay and necrosis dominated. **Our findings suggest that even at low concentrations, these pesticides could induce cytogenetic damage to human peripheral blood lymphocytes and in that manner have the impact on human health as well** (Gerić et al. 2012).

10. ENDOCRINOLOGICAL AND REPRODUCTIVE EFFECTS

Endocrine Disruption on androgen/estrogen receptors

Title: Endocrine disruptors provoke differential modulatory responses on androgen receptor and pregnane and xenobiotic receptor: Potential implications in metabolic disorders (2010)

ABSTRACT: A systematic comparison of the impact of some potential endocrine disruptors (EDs) on modulation of androgen receptor (AR) and pregnane and xenobiotic receptor (PXR) function was conducted in a multi-step analysis. Experiments with DDT treatment in mice model indicated that in testis AR and its regulated genes PEM and ODC levels are down-regulated, whereas in liver of same mice PEM is up-regulated while AR and ODC remain unchanged. On the contrary, PXR and its regulated genes CYP3A11 and MDR1 levels in mice liver were up-regulated while in testis PXR remained unchanged, CYP3A11 up-regulated and MDR1 were down-regulated. **Based on a novel "Biopit" concept it is speculated that long-term exposure to endocrine disrupting chemicals may influence the epigenetic profile of target cells via transcription factors thereby making them vulnerable to onset of chemically induced endocrine-related malignancies or metabolic disorders** (Chaturvedi et al. 2010).

Title: Effect of exposure to p,p'-DDE on male hormone profile in Mexican flower growers (2011)

ABSTRACT: Objectives: p,p'-Dichlorodiphenyldichloroethene (p,p'-DDE) acts as an androgen receptor antagonist, however data regarding its hormonal effects in men are limited. The objective of this study was to evaluate the association between serum levels of p,p'-DDE and reproductive hormone profile in Mexican male flower growers. Methods: A longitudinal study was carried out in a population of men working in the production of flowers and ornamental plants in two Mexican states during July-October 2004 (rainy season) and December 2004-May 2005 (dry season). A questionnaire including information on socioeconomic characteristics, tobacco and alcohol use, presence of chronic and acute diseases, occupational history and anthropometry was used and blood and urine samples were obtained. Serum levels of p,p'-DDE were analysed by gas chromatography; FSH, LH, testosterone, oestradiol, inhibin B and prolactin levels were measured by enzymatic immunoassay. Urinary levels of dialkylphosphates (DAPs) were analysed by gas chromatography. Associations between serum levels of p,p'-DDE and male reproductive hormones (both transformed to their natural logarithm) were evaluated using multivariate generalised estimating equation (GEE) models. Results: Median p,p'-DDE levels were 677.2 ng/g lipid (range 9.4-12 696.5) during the rainy season and 626.7 ng/g lipid (range 9.4-13 668.1) during the dry season. After adjusting for potential confounders (age, body mass index, state of residence and DAPs), p,p'-DDE levels were negatively associated with prolactin ($\beta=-0.04$; 95% CI -0.07 to -0.008) and testosterone ($\beta=0.04$; 95% CI -0.08 to 0.005) and positively with inhibin B ($\beta=0.11$; 95% CI 0.02 to 0.21). **Conclusion: These results indicate that p,p'-DDE can affect hypothalamic-pituitary-gonadal axis function in humans** (Blanco-Munoz et al. 2011).

Title: Changes in male hormone profile after occupational organophosphate exposure. A longitudinal study (2013)

ABSTRACT: There is a growing concern about the endocrine effects of long-term, low-level exposure to organophosphate (OP) compounds. Studies on experimental animals have found that OP pesticides have an impact on the endocrine system and a few clinical and epidemiological studies have also shown that OPs may affect the male hormone profile,

although results are inconsistent. We have evaluated the effect of exposure to OP pesticides, measured through urinary levels of six dialkylphosphate (DAP) metabolites, on male hormone profile in 136 floriculture workers from the State of Mexico and Morelos during two agricultural periods with different degree of pesticide exposure. Generalized estimated equations (GEE) models were developed and adjusted for several potential confounders, including PON1 enzyme activity, as a biomarker of susceptibility, and serum levels of p,p'-DDE, a metabolite of the pesticide DDT widely used in Mexico until 1999 for control of agricultural pests and malaria. Exposure of male floriculture workers to OP pesticides was associated with increased serum levels of follicle-stimulating hormone (FSH) and prolactin and with decreased serum testosterone and inhibin B levels. Among all DAPs tested, only DETP was inversely associated with luteinizing hormone (LH). Estradiol showed a marginally significant positive trend with DEP and DETP derivatives. **In conclusion, OP pesticides may have an impact on the endocrine function because of their potential to modify the male hormone profile as a function of the type of pesticide used as well as the magnitude of exposure** (Aguilar-Garduno 2013).

Title: Persistent Organochlorine Pollutants with Endocrine Activity and Blood Steroid Hormone Levels in Middle-Aged Men(2013)

ABSTRACT: Background: Studies relating long-term exposure to persistent organochlorine pollutants (POPs) with endocrine activities (endocrine disrupting chemicals) on circulating levels of steroid hormones have been limited to a small number of hormones and reported conflicting results. Objective: We examined the relationship between serum concentrations of dehydroepiandrosterone, dehydroepiandrosterone sulphate, androstenedione, androstenediol, testosterone, free and bioavailable testosterone, dihydrotestosterone, estrone, estrone sulphate, estradiol, sex-hormone binding globulin, follicle-stimulating hormone, and luteinizing hormone as a function of level of exposure to three POPs known to interfere with hormone-regulated processes in different way: dichlorodiphenyl dichloroethene (DDE), polychlorinated biphenyl (PCB) congener 153, and chlordecone. Methods: We collected fasting, morning serum samples from 277 healthy, non obese, middle-aged men from the French West Indies. Steroid hormones were determined by gas chromatography-mass spectrometry, except for dehydroepiandrosterone sulphate, which was determined by immunological assay, as were the concentrations of sex-hormone binding globulin, follicle-stimulating hormone and luteinizing hormone. Associations were assessed by multiple linear regression analysis, controlling for confounding factors, in a backward elimination procedure, in multiple bootstrap samples. **Results: DDE exposure was negatively associated to dihydrotestosterone level and positively associated to luteinizing hormone level. PCB 153 was positively associated to androstenedione and estrone levels. No association was found for chlordecone.** **Conclusions: These results suggested that the endocrine response pattern, estimated by determining blood levels of steroid hormones, varies depending on the POPs studied, possibly reflecting differences in the modes of action generally attributed to these compounds. It remains to be investigated whether this response pattern is predictive of the subsequent occurrence of disease** (Emeville et al. 2013).

Title: Distinct mechanisms of endocrine disruption of DDT-related pesticides toward estrogen receptor α and estrogen-related receptor γ (2012)

ABSTRACT: Dichlorodiphenyltrichloroethane (DDT) is ubiquitous in the environment, and the exposure to DDT and its related pesticides has long been linked to endocrine disruption. The mechanism of endocrine disruption toward targeted receptors, however, remains unclear. Probing the molecular recognition of DDT analogs by targeted receptors at the atomic level is critical for deciphering this mechanism. Molecular dynamics (MD) simulations were applied to probe the molecular recognition process of DDT and its five analogs, including dichlorodiphenyldichloroethylene (DDE), dichlorodiphenyldichloroethane (DDD), methoxychlor (MXC), p,p'-hydroxy-DDT (HPTE), and dicofol by human estrogen receptor (ER) α and human ER-related receptor (ERR) γ . Van der Waals interactions mainly drive the interactions of DDT analogs with ER α ligand-binding domain (LBD) and ERR γ LBD. Minor structural changes of DDT analogs in the number and position of chlorine and phenolic hydroxyl moiety cause differences in binding modes through aromatic stacking and hydrogen bonding and thus affect differently conformational changes of ER α LBD and ERR γ LBD. **The binding of DDT analogs affects the helix 12 orientation of ER α LBD but causes no rearrangement of helix 12 of ERR γ LBD. These results extend our understanding of how DDT analogs exert their estrogen-disrupting effects toward different receptors via multiple mechanisms** (Zhuang et al. 2012).

Title: Disruption of androgen receptor signaling in males by environmental chemicals (2011)

ABSTRACT: Androgen-disruptors are environmental chemicals in that interfere with the biosynthesis, metabolism or action of endogenous androgens resulting in a deflection from normal male developmental programming and reproductive tract growth and function. Since male sexual differentiation is entirely androgen-dependent, it is highly susceptible to androgen-disruptors. Animal models and epidemiological evidence link exposure to androgen disrupting chemicals with reduced sperm counts, increased infertility, testicular dysgenesis syndrome, and testicular and prostate cancers. Further, there appears to be increased sensitivity to these agents during critical developmental windows when male differentiation is at its peak. A variety of in vitro and in silico approaches have been used to identify broad classes of androgen disrupting molecules that include organochlorinated pesticides, industrial chemicals, and plasticizers with capacity to ligand the androgen receptor. The vast majority of these synthetic molecules act as anti-androgens. **This review will highlight the evidence for androgen disrupting chemicals that act through interference with the androgen receptor, discussing specific compounds for which there is documented in vivo evidence for male reproductive tract perturbations. This article is part of a Special Issue entitled 'Endocrine disruptors** (Luccio-Camelo and Prins 2011).

Title: Differential effects of the persistent DDT metabolite methylsulfonyl-DDE in nonstimulated and LH-stimulated neonatal porcine Leydig cells (2013)

Abstract: 3-Methylsulfonyl-DDE (MeSO₂-DDE) is a potent adrenal toxicant formed from the persistent insecticide DDT. MeSO₂-DDE is widely present in human plasma, milk and fat, and in tissues of marine mammals. In the present study, we investigated endocrine-disrupting properties of MeSO₂-DDE in primary neonatal porcine Leydig cells. Unstimulated and LH-stimulated cells were exposed to MeSO₂-DDE at concentrations ranging from 0.6 to 20 μ M for 48h. Cell viability, hormone secretion and expression of steroidogenesis related genes

were recorded. Secretion of testosterone and estradiol was increased in a concentration-dependent fashion in unstimulated Leydig cells, while in LH-stimulated cells, secretion of testosterone, estradiol and progesterone was decreased. The expression of important steroidogenic genes was down-regulated both in unstimulated and LH-stimulated cells. Notably, no significant impairment of cell viability occurred at any exposure except the highest concentration (20µM) in LH-stimulated cells. This indicated that the effects on hormone secretion and gene expression were not caused by cytotoxicity. **We conclude that the adrenal toxicant MeSO₂-DDE disrupts hormone secretion in a complex fashion in neonatal porcine Leydig cells. The different endocrine responses in unstimulated and LH-stimulated cells imply that the endocrine disruptive activity of MeSO₂-DDE is determined by the physiological status of the Leydig cells** (Castellanos et al. 2013).

Title: Cross-species conservation of endocrine pathways: A critical analysis of tier 1 fish and rat screening assays with 12 model chemicals (2013)

ABSTRACT: Many structural and functional aspects of the vertebrate hypothalamic-pituitary-gonadal (HPG) axis are known to be highly conserved, but the significance of this from a toxicological perspective has received comparatively little attention. High-quality data generated through development and validation of Tier 1 tests for the U.S. Environmental Protection Agency Endocrine Disruptor Screening Program (EDSP) offer a unique opportunity to compare responses of mammals versus fish to chemicals that may affect shared pathways within the HPG axis. The present study focuses on data generated with model chemicals that act (primarily) as estrogen receptor agonists (17α-ethynylestradiol, methoxychlor, bisphenol A), androgen receptor agonists (methyltestosterone, 17β-trenbolone), androgen receptor antagonists (flutamide, vinclozolin, p,p'-DDE), or inhibitors of different steroidogenic enzymes (ketoconazole, fadrozole, fenarimol, prochloraz). All 12 chemicals had been tested in the EDSP fish short-term (21d) reproduction assay and in one or more of the four in vivo Tier 1 screens with rats (uterotrophic, Hershberger, male and female pubertal assays). There was a high concordance between the fish and rat assays with respect to identifying chemicals that impacted specific endocrine pathways of concern. Although most chemicals were detected as positive in both rat and fish assays, eliminating data from one class of vertebrate or the other would weaken the battery. **For example, the effects of competitive inhibitors of steroid hormone synthesis were far more obvious in the fish assay, whereas the activity of androgen receptor antagonists was clearer in mammalian assays. The observations are significant both to the cross-species extrapolation of toxicity of HPG-active substances and the optimization of screening and testing frameworks for endocrine-disrupting chemicals** (Ankley and Gray 2013).

Endocrine Disruption and Obesity Development

Title: Endocrine-disrupting chemicals and obesity development in humans: A review (2011)

ABSTRACT: This study reviewed the literature on the relations between exposure to chemicals with endocrine-disrupting abilities and obesity in humans. The studies generally indicated that exposure to some of the endocrine-disrupting chemicals was associated with an increase in body size in humans. The results depended on the type of chemical, exposure

level, timing of exposure and gender. Nearly all the studies investigating dichlorodiphenyldichloroethylene (DDE) found that exposure was associated with an increase in body size, whereas the results of the studies investigating polychlorinated biphenyl (PCB) exposure were depending on dose, timing and gender. Hexachlorobenzene, polybrominated biphenyls, beta-hexachlorocyclohexane, oxychlordane and phthalates were likewise generally associated with an increase in body size. Studies investigating polychlorinated dibenzodioxins and polychlorinated dibenzofurans found either associations with weight gain or an increase in waist circumference, or no association. The one study investigating relations with bisphenol A found no association. Studies investigating prenatal exposure indicated that exposure in utero may cause permanent physiological changes predisposing to later weight gain. **The study findings suggest that some endocrine disruptors may play a role for the development of the obesity epidemic, in addition to the more commonly perceived putative contributors** (Tang-Peronard et al. 2011).

Title: Prenatal concentrations of polychlorinated biphenyls, DDE, and DDT and overweight in children: A prospective birth cohort study (2012)

ABSTRACT: Background: Recent experimental evidence suggests that prenatal exposure to endocrine-disrupting chemicals (EDCs) may increase postnatal obesity risk and that these effects may be sex or diet dependent. Objectives: We explored whether prenatal organochlorine compound (OC) concentrations [polychlorinated biphenyls (PCBs), dichlorodiphenyldichloroethylene (DDE), and dichlorodiphenyltrichloroethane (DDT)] were associated with overweight at 6.5 years of age and whether child sex or fat intakes modified these associations. Methods: We studied 344 children from a Spanish birth cohort established in 1997-1998. Overweight at 6.5 years was defined as a body mass index (BMI) z-score \geq 85th percentile of the World Health Organization reference. Cord blood OC concentrations were measured and treated as categorical variables (tertiles). Children's diet was assessed by food frequency questionnaire. Relative risks (RRs) were estimated using generalized linear models. Results: After multivariable adjustment, we found an increased RR of overweight in the third tertile of PCB exposure [RR = 1.70; 95% confidence interval (CI): 1.09, 2.64] and the second tertile of DDE exposure (RR = 1.67; 95% CI: 1.10, 2.55), but no association with DDT exposure in the population overall. Associations between overweight and PCB and DDE concentrations were strongest in girls (p-interaction between 0.01 and 0.28); DDT was associated with overweight only in boys. For DDT we observed stronger associations in children with fat intakes at or above compared with below the median, but this interaction was not significant (p-interaction > 0.05). **Conclusions: This study suggests that prenatal OC exposures may be associated with overweight in children and that sex and high-fat intake may influence susceptibility** (Valvi et al. 2012).

Title: Prenatal exposure to persistent organochlorines and childhood obesity in the U.S. collaborative perinatal project (2013)

ABSTRACT: Background: In some previous studies, prenatal exposure to persistent organochlorines such as 1,1,-dichloro-2,2-bis(p-chlorophenyl)ethylene (p,p'DDE),

polychlorinated biphenyls (PCBs), and hexachlorobenzene (HCB) has been associated with higher body mass index (BMI) in children. Objective: Our goal was to evaluate the association of maternal serum levels of β -hexachlorocyclohexane (β -HCH), p,p'DDE, dichlorodiphenyltrichloroethane (p,p'DDT), dieldrin, heptachlor epoxide, HCB, trans-nonachlor, oxychlordane, and PCBs with offspring obesity during childhood. Methods: The analysis was based on a subsample of 1,915 children followed until 7 years of age as part of the U.S. Collaborative Perinatal Project (CPP). The CPP enrolled pregnant women in 1959-1965; exposure levels were measured in third-trimester maternal serum that was collected before these organochlorines were banned in the United States. Childhood overweight and obesity were defined using age- and sex-specific cut points for BMI as recommended by the International Obesity Task Force. Results: Adjusted results did not show clear evidence for an association between organochlorine exposure and obesity; however, a suggestive finding emerged for dieldrin. Compared with those in the lowest quintile (dieldrin, $< 0.57 \mu\text{g/L}$), odds of obesity were 3.6 (95% CI: 1.3, 10.5) for the fourth and 2.3 (95% CI: 0.8, 7.1) for the highest quintile. Overweight and BMI were unrelated to organochlorine exposure. **Conclusions: In this population with relatively high levels of exposure to organochlorines, no clear associations with obesity or BMI emerged** (Cupul-Uicab et al. 2013).

Title: In utero DDT and DDE exposure and obesity status of 7-year-old Mexican-American children in the CHAMACOS cohort (2013)

ABSTRACT: Background: In utero exposure to endocrine disrupting compounds including dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) has been hypothesized to increase risk of obesity later in life. Objectives: The Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study is a longitudinal birth cohort of low-income Latinas living in a California agricultural community. We examined the relation of in utero DDT and DDE exposure to child obesity at 7 years of age. We also examined the trend with age (2, 3.5, 5, and 7 years) in the exposure-obesity relation. Methods: We included 270 children with o,p'-DDT, p,p'-DDT, and p,p'-DDE concentrations measured in maternal serum during pregnancy (nanograms per gram lipid) and complete 7-year follow-up data including weight (kilograms) and height (centimeters). Body mass index (BMI; kilograms per meter squared) was calculated and obesity was defined as ≥ 95 th percentile on the sex-specific BMI-for-age Centers for Disease Control and Prevention 2000 growth charts. Results: At 7 years, 96 (35.6%) children were obese. A 10-fold increase in o,p'-DDT, p,p'-DDT, or p,p'-DDE, was nonsignificantly associated with increased odds (OR) of obesity [o,p'-DDT adjusted (adj-) OR = 1.17, 95% CI: 0.75, 1.82; p,p'-DDT adj-OR = 1.19, 95% CI: 0.81, 1.74; p,p'-DDE adj-OR = 1.22, 95% CI: 0.72, 2.06]. With increasing age at follow-up, we observed a significant trend toward a positive association between DDT and DDE exposure and odds of obesity. **Conclusion: We did not find a significant positive relation between in utero DDT and DDE exposure and obesity status of 7-year-old children. However, given the observed trend with age, continued follow-up will be informative** (Warner et al. 2013).

Title: Alterations in T-lymphocyte sub-set profiles and cytokine secretion by PBMC of systemic lupus erythematosus patients upon in vitro exposure to organochlorine pesticides (2012)

ABSTRACT: Chronic exposure to organochlorine pesticides (OCP) has been suspected of causing immunoregulatory abnormalities that eventually lead to development and progression of systemic lupus erythematosus (SLE), but the role of these non-genetic stimuli has remained poorly understood. The objectives of the study were to quantify the levels of different OCP residues in the blood of SLE patients and to study the effects of in vitro treatment of peripheral blood mononuclear cells (PBMC) from these patients and healthy controls with OCP. Levels of different OCP residues in the blood were measured by gas-liquid chromatography. Isolated PBMC were treated in vitro with hexachlorocyclohexane (HCH), o,p'-dichlorodiphenyltrichloroethane (DDT), or phytohemagglutinin-M (PHA-M) for 72 h, then stained with different dye-labeled monoclonal antibodies to analyze alterations in T-lymphocytes using flow cytometry. Levels of different T(H)1 and T(H)2 cytokines were also estimated by ELISA. Significantly higher levels of p,p'-DDE and β -HCH were detected in the blood of SLE patients than in healthy controls. HCH exposure markedly increased the percentages of CD3(+)CD4(+) T-lymphocytes and expression of CD45RO(+) on CD4(+) and CD8(+) T-lymphocytes, but decreased CD4(+)CD25(+) T-lymphocytes in SLE patients. DDT exposure increased the percentages of CD3(+)CD4(+) T-lymphocytes and decreased those of CD4(+)CD25(+) T-lymphocytes in SLE patients as compared to healthy controls. No significant responsiveness of patient PBMC to PHA-M stimulation was observed indicating suppression of T-lymphocytes by these OCP. Further, both HCH and DDT decreased the levels of IL-2 and IFN γ but had no effect on IL-4 levels in SLE patients. DDT also increased significantly the levels of IL-10 in patients. **It is likely that higher levels and prolonged durations of exposure to HCH and DDT may significantly influence T-lymphocyte sub-sets and cytokine expression in vivo that could lead to the development or exacerbation of SLE** (Dar et al. 2012).

10.1 Diabetes mellitus

Summary: Several recent cross-sectional studies of different populations have demonstrated statistical associations between type 2 diabetes mellitus and DDT and/or DDE. However, in each case, the studies also show associations that are of equivalent or greater strength for other persistent compounds, so that DDT and DDE levels may be biomarkers for other exposures (most notably PCBs) that, in turn, are more strongly associated with type 2 diabetes. All these studies did look for possible confounding by obesity (con-currently or prior to diagnosis). Alternatively, the metabolic alterations associated with diabetes are known to alter fat metabolism, which can affect serum lipid levels not only of DDT and DDE, but also of other persistent organic pollutants. Therefore, these results should be interpreted with caution, and at this point, results are inconclusive.

Type 1

Title: A nested case-control study of intrauterine exposure to persistent organochlorine pollutants in relation to risk of Type 1 diabetes (2010)

ABSTRACT: Persistent organochlorine pollutants (POPs) have been suggested as a triggering factor for developing childhood type 1 diabetes. The aim of this case-control study was to assess possible impacts of in utero exposure to POPs on type 1 diabetes. **Methodology/Principal Findings:** The study was performed as a case-control study within a biobank in Malmö, a city located in the Southern part of Sweden. The study included 150 cases (children who had their diagnosis mostly before 18 years of age) and 150 controls, matched for gender

and day of birth. 2,2',4,4',5,5'-hexachlorobiphenyl (PCB-153) and the major DDT metabolite 1,1-dichloro-2,2-bis (p-chlorophenyl)-ethylene (p,p'-DDE) were used as biomarkers for POP exposure. When comparing the quartile with the highest maternal serum concentrations of PCB-153 with the other quartiles, an odds ratio (OR) of 0.73 (95% confidence interval [CI] 0.42, 1.27) was obtained. Similar results were obtained for p,p'-DDE (OR 0.56, 95% CI 0.29, 1.08). **Conclusions: The hypothesis that in utero exposure to POPs will trigger the risk for developing type 1 diabetes was not supported by the results. The risk estimates did, although not statistically significant, go in the opposite direction. However, it is not reasonable to believe that exposure to POPs should protect against type 1 diabetes** (Rignell-Hydbom et al. 2010).

Type 2

Title: Strong associations between low-dose organochlorine pesticides and type 2 diabetes in Korea (2010)

ABSTRACT: Low-dose organochlorine (OC) pesticides have recently been associated with type 2 diabetes in several non-Asian general populations. As there is currently epidemic type 2 diabetes in Asia, we investigated the associations between OC pesticides and type 2 diabetes in Koreans. Among subjects who participated in a community-based health survey, we randomly selected 40 diabetic patients and 40 normal controls. In the case of chemicals belonging to the DDT family, adjusted ORs in the 3rd tertile were in the range of 10.6 (95% CI 1.3-84.9) for p,p'-DDT to 12.7 (95% CI 1.9-83.7) for p,p'-DDE. **In this exploratory study with small sample, low-dose background exposure to OC pesticides was strongly associated with prevalent type 2 diabetes in Koreans even though absolute concentrations of OC pesticides were no higher than in other populations.** Asians may be more susceptible to adverse effects of OC pesticides than other races (Son et al. 2010).

Title: High prevalence of prediabetes and diabetes in a population exposed to high levels of an organochlorine cocktail (2010)

ABSTRACT: A heavily polluted area of Eastern Slovakia was targeted by the PCBRISK cross-sectional survey to search for possible links between environmental pollution and both prediabetes and diabetes. **Methods:** Associations of serum levels of five persistent organic pollutants (POPs), namely polychlorinated biphenyls (PCBs), 2,2'-bis(4-chlorophenyl)-1,1-dichloroethylene (p,p'-DDE), 2,2'-bis(4-chlorophenyl)-1,1,1-trichloro-ethane (p,p'-DDT), hexachlorobenzene (HCB) and β -hexachlorocyclohexane (β -HCH), with prediabetes and diabetes were investigated in 2,047 adults. Diabetes and prediabetes were diagnosed by fasting plasma glucose in all participants and by OGTT in 1,220 compliant participants. **Results:** Our population was stratified in terms of individual POPs quintiles and associations between environmental pollution, prediabetes and diabetes were investigated. Prevalence of prediabetes and diabetes increased in a dose-dependent manner, with individuals in upper quintiles of individual POPs showing striking increases in prevalence of prediabetes as shown by OR and 95% CI for PCBs (2.74; 1.92-3.90), DDE (1.86; 1.17-2.95), DDT (2.48; 1.77-3.48), HCB (1.86; 1.7-2.95) and β -HCH (1.97; 1.28-3.04). Interestingly, unlike PCBs, DDT and DDE, increased levels of HCB and β -HCH seemed not to be associated with increased

prevalence of diabetes. Nevertheless, individuals in the 5th quintile of the variable expressing the cumulative effect of all five POPs (sum of orders) had a more than tripled prevalence of prediabetes and more than six times higher prevalence of diabetes when compared with the 1st referent quintile. Conclusions/interpretation: **Increasing serum concentrations of individual POPs considerably increased prevalence of prediabetes and diabetes in a dose-dependent manner. Interaction of industrial and agricultural pollutants in increasing prevalence of prediabetes or diabetes is likely** (Ukropec et al. 2010).

Title: Exposure to bioaccumulative organochlorine compounds alters adipogenesis, fatty acid uptake, and adipokine production in NIH3T3-L1 cells (2011)

ABSTRACT: Exposure to the organochlorine compounds p, p'-dichlorodiphenyldichloroethylene (DDE) and oxychlordane have been associated with an increased prevalence of diabetes. Although the exact etiology of diabetes, especially type 2 diabetes, is not known, it is thought that adipose dysfunction plays a vital role in the progression of this disease. Thus, the present study examined whether exposure to these bioaccumulative compounds promotes adipocyte dysfunction including alterations in adipogenesis, fatty acid storage, and adipokine production within the adipocyte. We employed the NIH3T3-L1 cell line as a model for adipogenesis and mature adipocyte function. Exposure to DDE or oxychlordane prior to and throughout differentiation did not affect adipogenesis. In mature NIH3T3-L1 adipocytes, exposure to oxychlordane, DDE, or dieldrin had no effect on insulin-stimulated fatty acid uptake but did increase basal fatty acid uptake over a 24 h period. There was no observed effect of exposure to these compounds on lipolysis. Exposure to DDE significantly increased the release of leptin, resistin, and adiponectin from mature adipocytes with corresponding increases in expression of resistin and adiponectin. **Taken together, the current data suggest that exposure to these compounds, especially DDE, may promote some aspects of adipocyte dysfunction that are commonly associated with obesity and type 2 diabetes** (Howell and Magnum, 2011).

Title: Blood concentrations of persistent organic pollutants and prediabetes and diabetes in the general population of Catalonia (2012)

ABSTRACT: The aim was to analyze the effects of body mass index (BMI), low-dose exposure, mixtures of persistent organic pollutants (POPs), and lipid adjustment on the relationship between POP concentrations and diabetes and prediabetes in the general adult population of Catalonia (Spain). Serum concentrations of POPs were measured by gas chromatography with electron-capture detection in 886 participants in a health interview survey. The highest concentrations of all POPs analyzed were found in subjects who had diabetes. Levels were also higher in individuals with prediabetes than in subjects without the disorder. In models adjusted by age, sex and BMI, the prevalence of diabetes and prediabetes increased in a dose-dependent manner across quartiles of PCBs 118, 138, 153, and 180, and HCB. When models were further adjusted for lipids, the associations were slightly lower and statistically significant, the ORs for the upper quartile ranging from 2.0 to 2.8 (all p-values for linear trend <0.05). **Concentrations of p,p'-DDT, p,p'-DDE and β -HCH were not associated with diabetes or prediabetes. Increasing concentrations of PCBs and HCB were positively associated with diabetes and prediabetes. Only part of the association**

was due to age and BMI. Findings support the hypothesis that exposure to POPs may be a diabetogenic factor in both obese and nonobese individuals (Gasull et al. 2012).

Title: Adipose tissue concentrations of persistent organic pollutants and prevalence of type 2 diabetes in adults from Southern Spain (2013)

ABSTRACT: There is increasing evidence that environmental factors play an important role in the development of type 2 diabetes. Several persistent organic pollutants are suspected to contribute to the increasing prevalence and risk of type 2 diabetes. The aim of this study was to investigate the association of the body burden of three organochlorine pesticides and three polychlorinated biphenyls and the overall estrogenic activity with the risk of type 2 diabetes in a sample of adults from Southern Spain. Samples of adipose tissue and serum were obtained from 386 subjects undergoing non-cancer-related surgery and were extracted using validated methodologies. Residues of persistent organic pollutants were analyzed by means of high-resolution gas chromatography with a mass spectrometry detector in tandem mode. The overall estrogenicity of the adipose tissue extracts was measured by using the total effective xenoestrogen burden (TEXB) biomarker. Data on lifestyle, dietary habits, and health status were gathered from face-to-face interviews and clinical records. Statistical analyses were performed with unconditional logistic regression and different adjustment levels. **In the models adjusted for adipose tissue origin, sex, age, and body mass index, the 2nd and 3rd tertiles of adipose tissue concentrations of p, p'-dichlorodiphenyldichloroethylene (p,p'-DDE) were positively associated with the risk of diabetes [odds ratios (95% confidence interval)=3.6 (0.8-17.3) and 4.4 (1.0-21.0), respectively].** A positive association with B-hexachlorocyclohexane was also found when body mass index and adipose tissue origin were removed from the models, with odds ratios (95% confidence interval) of 3.3 (1.0-10.4) and 5.5 (1.7-17.3), for the 2nd and 3rd tertiles of exposure, respectively. **In addition, a statistically significant interaction was observed between p,p'-DDE and body mass index, such that the risk of diabetes increased with tertiles of exposure in a linear manner in non-obese subjects but not in the obese, in whom an inverted U-shape pattern was observed (Arrebola et al. 2013)**

Title: Evaluation of the association between persistent organic pollutants (POPs) and diabetes in epidemiological studies: A national toxicology program workshop review (2013)

ABSTRACT: Background: Diabetes is a major threat to public health in the United States and worldwide. Understanding the role of environmental chemicals in the development or progression of diabetes is an emerging issue in environmental health. Objective: We assessed the epidemiologic literature for evidence of associations between persistent organic pollutants (POPs) and type 2 diabetes. Methods: Using a PubMed search and reference lists from relevant studies or review articles, we identified 72 epidemiological studies that investigated associations of persistent organic pollutants (POPs) with diabetes. We evaluated these studies for consistency, strengths and weaknesses of study design (including power and statistical methods), clinical diagnosis, exposure assessment, study population characteristics, and identification of data gaps and areas for future research. Conclusions: Heterogeneity of the studies precluded conducting a meta-analysis, but the overall evidence is sufficient for a positive association of some organochlorine POPs with type 2 diabetes. Collectively, these data are not sufficient to establish causality. **Initial data mining revealed that the strongest positive correlation of diabetes with POPs occurred with organochlorine compounds,**

such as trans-nonachlor, dichlorodiphenyldichloroethylene (DDE), polychlorinated biphenyls (PCBs), and dioxins and dioxin-like chemicals. There is less indication of an association between other nonorganochlorine POPs, such as perfluoroalkyl acids and brominated compounds, and type 2 diabetes. **Experimental data are needed to confirm the causality of these POPs, which will shed new light on the pathogenesis of diabetes. This new information should be considered by governmental bodies involved in the regulation of environmental contaminants** (Taylor et al. 2013).

Title: Pesticides usage in agriculture among rural women in Egypt: Association between serum organo-chlorine pesticide residues and occurrence of diabetes (2013)

Organochlorine pesticides were widely used in Egypt; large quantities had been released into the environment, where they became persistent substances both in the environment and in the food chain. The non organized use of pesticides in Egypt has caused immense damage to the environment and human health. Recent studies have reported an association between exposure to organo-chlorines pesticides (OCPs) and impaired blood-glucose regulation. The study aimed to investigate the relation between exposure to specific agricultural pesticides and diabetes incidence among some Egyptian women. The population study consisted of 51 rural women, who help their families in agriculture. For all participants in the study, questionnaires were filled up and, blood samples were obtained for determination of blood glucose levels and of OC pesticides residues. The dieldrin and DDD residues were found almost in all samples, followed by the heptachlor, heptachlor-epoxide and the aldrin respectively and finally the DDE. There was only a significant positive correlation between the heptachlor residue and the blood glucose level of the participants. **Evaluation of the attitudes and behavior of the studied population showed a significant association between the heptachlor and DDE residues in the sera of women who didn't use or have pesticides in their home. This can confirm that the presence of OC pesticides in several environmental compartment like food and soil, may pose another risk factor for the human health. These findings may have relevance to the general population, who suffer greatly from environmentally persistent compounds and the increasing prevalence of diabetes and a further extended study is needed** (Sharaf et al. 2013).

10.2 Thyroid effects

Summary: The findings on thyroid hormones and TSH are inconsistent. For adults, generally, there was only one study (Meeker et al., 2007) that showed associations between DDE levels and decreased thyroid hormones and increased TSH levels. Three studies (Sugiura-Ogasawara et al., 2003; Takser et al., 2005; Chevrier et al., 2008) looked at thyroid hormone status during pregnancy and had mixed results for DDE and either decreased T_3 or decreased T_4 or free T_4 . Three studies of children (Takser et al., 2005; Asawasinsophon et al., 2006a; Alvarez-Pedrerol et al., 2008a) had mixed results, with one showing decreased T_4 with DDE and not DDT and another decreased T_3 with DDT and not DDE (the third showed that DDT and DDE levels were not related to TSH concentrations in newborns). Two studies of older children showed mixed effects. One (Alvarez-Pedrerol et al., 2008b) showed decreased T_3 with higher DDT (but not DDE) at birth, and the other (Schell et al., 2008) did not show effects with concurrent exposures. A case-control study (Nagayama et al., 2007) associated higher breast milk DDT and DDE (but also other persistent chemicals) with congenital hypothyroidism. Overall, the human studies for DDT/DDE and thyroid hormones are inconclusive.

Title: Prenatal exposure to organochlorine compounds and neonatal thyroid stimulating hormone levels (2010)

ABSTRACT: OC concentrations in umbilical cord serum and TSH in blood of newborns were measured shortly after birth as it had been suggested that prenatal exposure to some organochlorine compounds (OCs) may adversely affect thyroid function and may, therefore, impair neurodevelopment. This study included 453 infants born between 2004 and 2006. Associations between neonatal TSH levels and prenatal OC exposure adjusted for covariates were assessed using multivariate linear regression analyses. **No statistically significant association was found between 4,4'DDT or 4,4'DDE and TSH at birth** (Lopez-Espinosa et al. 2010).

Title: Hypothyroidism and Pesticide Use among Male Private Pesticide Applicators in the Agricultural Health Study

ABSTRACT: OBJECTIVE: Evaluate the association between thyroid disease and use of insecticides, herbicides, and fumigants/fungicides in male applicators in the Agricultural Health Study. METHODS: We examined the association between use of 50 specific pesticides and self-reported hypothyroidism, hyperthyroidism, and "other" thyroid disease among 22,246 male pesticide applicators. RESULTS: There was increased odds of hypothyroidism with ever use of the herbicides 2,4-D (2,4-dichlorophenoxyacetic acid), 2,4,5-T (2,4,5-trichlorophenoxyacetic acid), 2,4,5-TP (2,4,5-trichlorophenoxy-propionic acid), alachlor, dicamba, and petroleum oil. Hypothyroidism was also associated with ever use of eight insecticides: organochlorines chlordane, dichlorodiphenyltrichloroethane (DDT), heptachlor, lindane, and toxaphene; organophosphates diazinon and malathion; and the carbamate carbofuran. Exposure-response analysis showed increasing odds with increasing level of exposure for the herbicides alachlor and 2,4-D and the insecticides aldrin, chlordane, DDT, lindane, and parathion. CONCLUSION: **There is an association between hypothyroidism and specific herbicides and insecticides in male applicators, similar to previous results for spouses** (Goldner et al. 2013).

10.2.1 In vitro

10.2.3 Humans

10.3 Reproductive and developmental toxicity

10.3.1 In vitro

10.3.2 Laboratory animals

10.3.2.1 Multigeneration studies

Summary: From multigeneration studies, there is little evidence for reproductive toxicity of DDT in mammalian species (mice, rats, dogs). One study reported increased mortality of mouse pups with DDT dosing of 33 mg/kg bw per day, and a second found earlier puberty in dogs dosed at 10 mg/kg bw per day.

10.3.2.2 Effects on fertility in males

Summary: There are adverse effects on multiple male reproductive parameters and hormones with increasing exposure to DDT (≥ 50 mg/kg bw per day for 10 days) and DDE (200 mg/kg bw per day for 4 or 5 days). DDE induces anti-androgenic effects in vitro and in vivo. Anti-androgenic effects have been described in male rats after high exposure in utero and during lactation. DDT binds to the ER α and is a weak estrogen agonist.

Title: p, p'-DDE induces apoptosis and mRNA expression of apoptosis-associated genes in testes of pubertal rats (2013)

ABSTRACT: One, 1-dichloro-2, 2 bis(p-chlorophenyl) ethylene (p, p'-DDE), the major metabolite of 2, 2-bis(4-chlorophenyl)-1, 1, 1-trichloroethane (DDT), is a known persistent organic pollutant and male reproductive toxicant. It has antiandrogenic effect. However, the mechanism by which p, p'-DDE exposure causes male reproductive toxicity remains unknown. To elucidate the mechanism underpinning the testicular effects of p, p'-DDE, we sought to investigate apoptotic effects and mRNA expression of apoptosis-associated genes in the testis of pubertal rats, including Fas, FasL, calpain-1, cytochrome c, Bax, Bcl-w, Bak, and caspase-3, -8, -9, -12. Animals were administered with different doses of p, p'-DDE (0, 20, 60, 100 mg/kg body weight) every other day by intraperitoneal injection for 10 days. The results indicated that p, p'-DDE exposure at over 20 mg/kg body weight showed the induction of apoptotic cell death. p, p'-DDE could induce decrease in SOD and GSH-Px activity of serum in 60 mg/kg body weight group. Significant elevations in the mRNA levels of Fas, FasL, calpain-1, cytochrome c, Bax, Bak, and caspase-3, -8, -9, -12 were observed in testis of rat treated with p, p'-DDE. **Taken together, these results lead us to speculate that in vivo exposure to p, p'-DDE might induce testicular apoptosis in pubertal rats through the involvement of Fas/FasL, mitochondria and endoplasmic reticulum-mediated pathways** (Shi et al. 2013).

10.3.2.3 Effects on fertility in females

Summary: There are too few studies of effects on fertility of females to make a firm conclusion.

10.3.2.4 Developmental toxicity Fetal Growth

Summary: The available studies are too limited to make conclusions on possible effects of DDT/DDE on overall embryo-fetal development.

Developmental Neurotoxicity

Summary: No guideline developmental neurotoxicity studies were available. The studies by Eriksson and co-workers (e.g. Eriksson et al., 1990b, 1992) provide evidence that exposure of neonatal mice to DDT (a single intragastric dose of 0.5 mg/kg bw) during a specific stage of development (for the mouse, at PND 10) caused significant neurochemical and functional neurodevelopmental changes, including variation in muscarinic acetylcholine receptor density in the cerebral cortex and increases in spontaneous motor activity, indicative of a relative inability to habituate to new surroundings.

10.3.2.5 Reproductive endocrine effects

Summary: Shortened anogenital distance has been consistently observed in Long-Evans rats and in single studies in two other rat strains at dose levels of 100–200 mg/kg bw per day. A single rabbit study with DDT (at 90 mg/kg bw per day) showed increased incidence of cryptorchidism. A single study in two strains of rats showed no significant increase in hypospadias after dosing with DDE.

10.3.3 Humans

10.3.3.1 Male reproductive functions and hormone levels

Summary: Associations have been reported between adverse effects on multiple semen parameters and increasing exposure to DDE, particularly among men with recent or current use and higher exposure levels (Table 6). It is difficult to ascertain causality of exposure in cross-sectional studies, but the evidence suggests that several different semen parameters were negatively affected by increasing DDE levels. Human data are inadequate to assess male fertility and fecundity with regards to DDT/DDE exposures at population levels. A recent study has indicated that there may be a relationship between occupational DDT exposure and higher serum estradiol levels in men. A single human

Title: Pesticide exposure and decreased sperm count (2010)

ABSTRACT: Introduction: Recent studies have demonstrated a possible decline in semen quality in men. One of the reasons for this is due, in part, to exogenous chemical substances, some of which have hormonal activity, and are considered to be endocrine-disrupting chemicals. Pesticides can be included in this group. Material and methods: These studies have been criticized both for errors in selecting the study group as well as for the analytical methods employed. The objective of our study is to evaluate the concentration of pesticides in blood samples-in addition to the sperm count and semen quality parameters (according to criteria set out by the W.H.O.) in a population of 273 healthy men with an average age of 20.7 years; all from Southern Spain and recruited in collaboration with the University of Almeria. Results: **Out of the total of 224 serum samples available, at least one pesticide was quantified per sample, with an average of 11 pesticides per sample; the most frequent being p,p'-DDE, present in 95.98% of the samples. Only in the case of endosulfan sulphate (present in 45.1% of the volunteers) was there a strong reduction tendency in the number of spermatozoa of more than 1.23 million, reaching statistical significance(P=0.009), with a 95% confidence interval of -1.43 to -1.05.** As far as the number of motile spermatozoa were concerned, it was also only with endosulfan sulphate that a statistically significant reduction of 1.23 million (P=0.02) in the total number appeared, with a 95% confidence interval of -1.47 to -1.04) (Avivar Oyonarte 2010).

Title: Environmental exposure to polychlorinated biphenyls and p,p'-DDE and sperm sex-chromosome disomy (2012)

ABSTRACT: Background: Chromosomal abnormalities contribute substantially to reproductive problems, but the role of environmental risk factors has received little attention. Objectives: We evaluated the association of polychlorinated biphenyl (PCB) and dichlorodiphenyldichloroethylene (p,p'-DDE) exposures with sperm sex-chromosome disomy. Methods: We conducted a cross-sectional study of 192 men from subfertile couples. We used multiprobe fluorescence in situ hybridization (FISH) for chromosomes X, Y, and 18 to determine XX, YY, XY, and total sex-chromosome disomy in sperm nuclei. Serum was analyzed for concentrations of 57 PCB congeners and p,p'-DDE. Poisson regression models were used to calculate incidence rate ratios (IRRs) for disomy by exposure quartiles, controlling for demographic characteristics and semen parameters. Results: The median percent disomy was 0.3 for XX and YY, 0.9 for XY, and 1.6 for total sex-chromosome disomy. We observed a significant trend of increasing IRRs for increasing quartiles of p,p'-DDE in XX, XY, and total sex-chromosome disomy, and a significant trend of increasing IRRs for increasing quartiles of PCBs for XY and total sex-chromosome disomy; however, there was a significant inverse association for XX disomy. Conclusions: **Our findings suggest that exposure to p,p'-DDE may be associated with increased rates of XX, XY, and total sex-chromosome disomy, whereas exposure to PCBs may be associated with increased rates of YY, XY, and total sex-chromosome disomy. In addition, we observed an inverse association between increased exposure to PCBs and XX disomy. Further work is needed to confirm these findings** (McAuliffe et al. 2012)

Title: Environmental and occupational pesticide exposure and human sperm parameters: a systematic review (2013)

ABSTRACT: Of continuing concern are the associations between environmental or occupational exposures to pesticides and semen quality parameters. Prior research has indicated that there may be associations between exposure to pesticides of a variety of classes and decreased sperm health. The intent of this review was to summarize the most recent evidence related to pesticide exposures and commonly used semen quality parameters, including concentration, motility and morphology. The recent literature was searched for studies published between January 2007 and August 2012 that focused on environmental or occupational pesticide exposures. Included in the review are 17 studies, 15 of which reported significant associations between exposure to pesticides and semen quality indicators. Two studies also investigated the roles genetic polymorphisms may play in the strength or directions of these associations. Specific pesticides targeted for study included dichlorodiphenyltrichloroethane (DDT), hexachlorocyclohexane (HCH), and abamectin. Pyrethroids and organophosphates were analyzed as classes of pesticides rather than as individual compounds, primarily due to the limitations of exposure assessment techniques. **Overall, a majority of the studies reported significant associations between pesticide exposure and sperm parameters. A decrease in sperm concentration was the most commonly reported finding among all of the pesticide classes investigated. Decreased motility was also associated with exposures to each of the pesticide classes, although these findings were less frequent across studies. An association between pesticide exposure and sperm morphology was less clear, with only two studies reporting an association. The evidence presented in this review continues to support the hypothesis that exposures to pesticides at environmentally or occupationally relevant levels may be associated with decreased sperm health.** Future work in this area should focus on associations between specific pesticides or metabolic products and sperm quality parameters. Analysis of effects of varying genetic characteristics, especially in genes related to pesticide metabolism, also needs further attention (Martenies and Perry 2013).

10.3.3.2 Female reproductive functions

a) Fertility/Fecundity

Summary: The available data are inadequate to evaluate the effect of prenatal exposure to DDT or DDE on fertility or fecundity as measured by time to pregnancy.

Title: Association of hexachlorobenzene (HCB), dichlorodiphenyl-trichloroethane (DDT), and Dichlorodiphenyldichloroethylene (DDE) with in vitro fertilization (IVF) outcomes (2012)

ABSTRACT: Background: Hexachlorobenzene (HCB), dichlorodiphenyltrichloroethane (DDT), and dichlorodiphenyldichloroethylene (DDE) are persistent chlorinated pesticides with endocrine activity that may adversely affect the early stages of human reproduction. Objective: Our goal was to determine the association of serum levels of HCB, DDT, and DDE with implantation failure, chemical pregnancy, and spontaneous abortion in women undergoing in vitro fertilization (IVF) from 1994 to 2003. Methods: Levels of HCB and

congeners of DDT and DDE were measured in serum collected during the follicular phase. Multivariable-adjusted statistical models accommodating multiple outcomes and multiple cycles per woman were used to estimate the relation between serum pesticide levels and IVF outcomes. Results: A total of 720 women with a mean \pm SD age 35.4 ± 4.2 years at enrollment contributed 774 IVF cycles. All samples had detectable levels of HCB, DDT, and DDE, with median levels of 0.087 ng/g serum for HCB, 1.12 ng/g serum for total DDT, and 1.04 ng/g serum for p,p'-DDE. Compared with the lowest quartile (Q1) of HCB, the lipid- and multivariable-adjusted odds ratio (OR) for failed implantation was significantly elevated for those with higher HCB quartiles [Q2-Q4; adjusted ORs: for Q2, 1.71; 95% confidence interval (CI): 1.03, 2.82; for Q3, 2.30; 95% CI: 1.39, 3.81; for Q4, 2.32; 95% CI: 1.38, 3.90] and showed a significantly increasing trend ($p = 0.001$). **No statistically significant associations were observed between DDT/DDE and IVF outcomes or between HCB and chemical pregnancy or spontaneous abortion.** Conclusions: Serum HCB concentrations were on average lower than that of the general U.S. population and associated with failed implantation among women undergoing IVF (Mahalingaiah et al. 2012).

Title: Organochlorine pesticides, polychlorinated biphenyls, seafood consumption, and time-to-pregnancy (2013)

ABSTRACT: BACKGROUND: People in developed countries are widely exposed to low levels of organochlorine pesticides, polychlorinated biphenyls (PCBs), and polybrominated diphenyl ethers (PBDEs). Seafood is a major contributor to PCB exposure. Toxicity of those various pollutants to reproductive and endocrine functions raises questions about possible effects on fertility. We explored whether serum levels of these pollutants and seafood consumption were associated with the fertility of couples enrolled in a French birth cohort (PELAGIE). **METHODS:** Time-to-pregnancy was investigated in 3,421 pregnant women by asking how many months they had taken to conceive. Levels of 14 organochlorine pesticides, 12 PCBs, and 10 PBDE compounds were measured in cord blood serum from a random subcohort ($n = 394$). Mercury concentrations measured in maternal hair were considered as a potential coexposure. Fecundability odds ratios (ORs) were estimated from multivariate discrete-time Cox proportional hazard models. **RESULTS:** Shellfish consumption was associated with longer time-to-pregnancy (fecundability OR \geq twice/week vs. $<$ twice/month = 0.71 [95% confidence interval = 0.60-0.83]), but fish consumption was not. Time-to-pregnancy increased with increasing serum levels for most of the compounds studied (for total PCBs >0.410 μ g/L vs. <0.266 μ g/L, fecundability OR = 0.46 [0.32-0.66]). In multiple sensitivity analyses, reduced fecundability was most consistently associated with shellfish consumption, p,p'-DDE, total PCBs, PCB153, and PCB187. Models that simultaneously included multiple coexposure factors led to similar conclusions. **CONCLUSIONS: Our findings were robust in sensitivity analyses, including analysis restricted to primiparous women. These results suggest that PCBs, p,p'-DDE, and other shellfish contaminants may impair human fertility** (Chevrier et al. 2013).

b) Menstrual cycle function

Summary: One study found that higher serum DDT and DDE levels were associated with decreased estrogen and progesterone levels, and another study reported decreased length of the luteal phase of menstrual cycles and lowered luteal phase progesterone metabolite levels.

c) Lactation

Summary: The evidence linking duration of lactation with DDE and DDT exposure is inconsistent.

Title: Serum persistent organic pollutants and duration of lactation among Mexican-American women (2010)

ABSTRACT: Research suggests that estrogenic endocrine-disrupting chemicals interfere with lactation. **Methods and Results.** We measured selected organochlorines and polychlorinated biphenyls (p, p' -DDE, p, p' -DDT, o, p' -DDT, -hexachlorocyclohexane, hexachlorobenzene, and PCBs 44, 49, 52, 118, 138, 153, and 180) in serum from 366 low-income, Mexican-American pregnant women living in an agricultural region of California and assessed breastfeeding duration by questionnaires. There was an associations for two potentially estrogenic POPs with lengthened lactation duration (HR [95 CI]: 0.6 [0.4, 0.8] for p, p' -DDE & 0.8 [0.6, 1.0] for PCB 52). Associations between antiestrogenic POPs (PCBs 138 and 180) and shortened lactation duration were attributed to a lactation history bias.

Conclusion: Estrogenic POPs were not associated with shortened lactation duration, but may be associated with longer lactation duration (Eskenazi et al. 2010).

d) Menopause

Summary: A single study suggests that high exposure to DDT and its metabolites is associated with earlier age at meno-pause. However, this study did not include any prospective measures of DDT exposure, and early menopause per se may cause increased DDT or DDE levels (e.g. by causing changes in body fat distribution).

10.3.3.3 Developmental effects

a) Spontaneous Abortion

Summary: Two cohort studies indicated an association between increasing DDT and DDE levels and fetal loss.

Title: Fetal loss and maternal serum levels of 2,2',4,4',5,5'-hexachlorobiphenyl (CB-153) and 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (p,p'-DDE) exposure: A cohort study in Greenland and two European populations (2010)

ABSTRACT: Background. In the present study, the aim is to examine the risk of fetal loss related to environmental 2,2',4,4',5,5'-hexachlorobiphenyl (CB-153) or 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (p,p'-DDE) exposure. **Methods.** We related LC/MS/MS measurements of CB-153 and p,p'-DDE in serum samples to interview-data on previous fetal loss in populations of pregnant women from Poland, Ukraine and Greenland. **Results.** In total, 1710 women were interviewed, and 678 of these had at least one previous pregnancy. The risk of ever experiencing a fetal loss increased at higher levels of CB-153 and p,p'-DDE exposure, with an adjusted odds ratio (OR) of 2.4; confidence interval (CI) (1.1-5.5) for CB-153>200 ng/g lipid compared to 0-25 ng CB-153/g lipid and OR of 2.5 CI (0.9-6.6) for p,p'-DDE>1500 ng/g lipid compared to 0-250 ng DDE/g lipid. However, no clear dose response associations were observed. The results further suggest that high level of organochlorine serum concentrations may be related to repeated loss. **Conclusions. The risk of fetal loss may increase at higher levels of CB-153 and p,p'-DDE exposure, although lack of dose**

response and inconsistencies between countries did not allow for firm conclusions (Toft et al. 2010).

b) Gestational age/preterm birth

Summary: The strongest epidemiological study (Longnecker et al., 2001) suggests an association of elevated maternal serum DDE levels with reduced gestational age and increased rates of small-for-gestational-age babies. Inconsistent results on association between DDT/DDE levels and gestational age were reported in other studies.

Title: Persistent organochlorine compounds in fetal and maternal tissues: Evaluation of their potential influence on several indicators of fetal growth and health (2011)

ABSTRACT: Some organochlorine compounds, such as polychlorinated biphenyls (PCBs), have a tendency to bioaccumulate in humans and predators at the top of the food chain. We have recently confirmed the transplacental transfer of these compounds and the present study has been designed on the same material with the aim of investigating their potential health effects on newborns from 70 pregnant women, resident in a Northern Italy industrial town. Organochlorine compounds [namely, p,p'-dichlorodiphenyltrichloroethane (p,p'-DDT), p,p'-dichlorodiphenyldichloroethene (p,p'-DDE), hexachlorobenzene (HCB), and PCBs] have been analyzed both in cord and maternal serum, placenta, and maternal subcutaneous adipose tissue by GC-MSD. p,p'-DDT levels in the adipose tissue resulted significantly ($p < 0.05$) related to birth length. **Mothers of neonates born by preterm programmed caesarean delivery showed significantly ($p < 0.005$ for both) higher serum p,p'-DDE serum concentrations and p,p'-DDT levels in the adipose tissue, as compared to mothers delivering at term** (Bergonzoni et al. 2011).

c) Fetal Growth

Summary: Available evidence does not suggest an association between DDT and/or DDE and fetal growth restriction.

Title: Prenatal exposure to organochlorine compounds and birth size (2011)

ABSTRACT: OBJECTIVE: To investigate the possible association between birth size and cord concentrations of some organochlorine compounds (OCs), including 4,4'-dichlorodiphenyltrichloroethane (DDT), 4,4'-1,1-dichloro-2,2-bis(p-dichlorodiphenyl)ethylene (DDE), hexachlorobenzene (HCB), β -hexachlorocyclohexane (β -HCH), 4 polychlorinated biphenyl (PCB) congeners (118, 138, 153, and 180), and their sum (Σ PCBs) in a birth cohort in Valencia, Spain. **STUDY DESIGN:** A total of 494 mothers and their newborns (born 2003-2006) participated in the study. Multivariate linear regression analyses were performed between birth weight, length, or head circumference and OC concentrations. **RESULTS:** Median concentrations of 4,4'-DDT, 4,4'-DDE, HCB, β -HCH, and Σ PCBs were 0.02, 0.46, 0.22, 0.09, and 0.35 ng/mL, respectively. For birth weight there was a significant decrease of 63 and 107 g for each 10-fold increase in cord serum 4,4'-DDT and 4,4'-DDE concentrations, and a marginally significant decrease of 79 and 53 g for each 10-fold increase in HCB and β -HCH concentrations. A significant decrease of 0.39 cm in birth length was found for each 10-fold increase in HCB concentrations. For newborns with cord 4,4'-DDT concentrations above the median there was a significant decrease of 0.26 cm in

birth head circumference. **CONCLUSIONS: These results reveal that prenatal exposure to some OCs could impair the anthropometric development of the fetus, reducing the birth weight, length, and head circumference** (Lopez-Espinosa et al. 2011).

Title: Association of maternal serum concentrations of 2,2', 4,4' 5,5' -hexachlorobiphenyl (CB-153) and 1,1-dichloro-2,2-bis (p-chlorophenyl)-ethylene (p,p'-DDE) levels with birth weight, gestational age and preterm births in Inuit and European populations (2010)

ABSTRACT: Background: Epidemiological studies on the association between maternal exposure to persistent organic pollutants (POPs) and fetal growth alteration report inconsistent findings which weights in favor of additional studies. Methods: Blood samples were collected from interviewed pregnant women in Greenland (572), Kharkiv (611) and Warsaw (258) and were analyzed for CB-153 and p,p'-DDE by gas chromatography-mass spectrometry. Data on birth weight, gestational age and preterm birth were obtained for 1322 singleton live births. We examined the association between natural log-transformed serum POPs concentration and birth weight and gestational age using multiple linear regression and the association with prematurity using logistic regression controlling for potential confounding factors. Results: The median serum concentrations of CB-153 and p,p'-DDE were for Inuit mothers 105.6 and 298.9, for Kharkiv mothers 27.0 and 645.4 and for Warsaw mothers 10.7 and 365.2 ng/g lipids, respectively. Increase in CB-153 concentration by one unit on the log scale in Inuit mothers serum was associated with significant decrease in infant birth weight of -59 g and gestational age by -0.2 week. Decreases observed in the cohorts in Kharkiv (-10 g and -0.1 week) and in Warsaw (-49 g and -0.2 week) were not statistically significant. Increase in p,p'-DDE concentration by one unit on the log scale was associated with a statistically significant decrease in infant birth weight of -39.4g and -104.3 g and shortening of gestational age of -0.2 week and -0.6 week in the Inuit and Warsaw cohorts, respectively. In the Kharkiv cohort decrease in birth weight (-30.5 g) was not significant, however a shortening of gestational age of -0.2 week per increase in p,p'-DDE concentration by one unit on the log scale was of the borderline significance. **There was no significant association between CB-153 and p,p'-DDE concentrations and risk of preterm birth however, in all cohorts the odds ratio was above 1. Conclusions: In utero exposure to POPs may reduce birth weight and gestational age of newborns however, new insights as to why results vary across studies were not apparent** (Wojtyniak et al. 2010).

Title: Dichlorodiphenyltrichloroethane (DDT), DDT metabolites and pregnancy outcomes (2013)

ABSTRACT: Organochlorine pesticides (OCPs) are persistent endocrine disruptors. OCPs cross the placenta; this prenatal exposure has been associated with adverse pregnancy outcomes. We investigated associations between prenatal exposure to OCPs and gestational age and birth weight in 600 infants born between 1960 and 1963. The primary OCP was 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (p,p'-DDT), its primary metabolite, 1,1'-dichloro-2,2'-bis(p-chlorophenyl)ethylene (p,p'-DDE) and the contaminant, 1,1,1-trichloro-2-(p-chlorophenyl)-2-(o-chlorophenyl)-ethane (o,p'-DDT). **Regression analysis indicated that for each natural log unit increase in p,p'-DDT, birth weight increased by 274. g (95% CI: 122, 425) when controlling for p,p'-DDE and o,p'-DDT. At a given level of**

p,p'-DDT exposure, o,p'-DDT and p,p'-DDE were associated with decreased birth weight. p,p'-DDE was negatively associated with length of gestation, controlling for p,p'-DDT and o,p'-DDT. These findings suggest opposing associations between exposure to p,p'-DDT and p,p'-DDE and birth weight. We did not find evidence to support mediation by maternal thyroid hormone status nor that the association differed by sex (Kezios et al. 2013).

Title: Levels of DDT and its metabolites in placenta, maternal and cord blood and their potential influence on neonatal anthropometric measures (2012)

ABSTRACT: Previous studies of in utero exposure to dichlorodiphenyltrichloroethane (DDT) have shown mixed results for the harmful effects on fetal growth and development. This cross-sectional study was designed to: (1) examine the extent of DDT exposure in 1578 women, aged 28.5 ± 6.0 who delivered between June 2005 and 2006 in the area of Al-Kharj, Saudi Arabia; and (2) assess its influence on neonatal anthropometric measurement of newly born babies. DDT and its metabolites, namely 1,1-dichloro-2,2-bis (p-chlorophenyl) ethylene (p,p'-DDE), 1,1-dichloro-2,2-bis (p-chlorophenyl) ethane (p,p'-DDD) and 1,1,1-trichloro-2,2,2-bis (p-chlorophenyl) ethane (p,p'-DDT) were measured in cord and maternal serum as well as placenta by Gas Chromatography coupled with an Electron Capture Detector (GC/ECD). p,p'-DDE was detected in 28.3% of cord and 54.4% of maternal serum, reflecting past exposure, whereas the p,p'-DDT was only found in 0.46% cord and 1.2% maternal samples. As expected the p,p'-DDE cord levels ($0.197 \pm 0.961 \mu\text{g/L}$) were 2.8 times lower than the maternal levels ($0.551 \pm 1.778 \mu\text{g/L}$), and both were significantly correlated ($r=0.517$) suggesting its transplacental transfer. The picture was different in placental tissues. p,p'-DDE and p,p'-DDT were detected in 84% and 99% of placental tissues, with the highest p,p'-DDT in placental tissues ($29.62 \pm 158.282 \mu\text{g/kg dry wt.}$) compare to p,p'-DDE ($10.167 \pm 18.851 \mu\text{g/kg dry wt.}$). In general, the presence of DDT metabolites in our participants indicates that these chemicals are still relevant despite the fact that they have been banned or restricted in the study area for many years. **Our results support the view for an association between low in utero exposure to DDT and the anthropometric development of the fetus leading to a reduction in its head circumference, crown-heel length, birth weight and birth height. Since the reduction in these measures was independent of gestational age and/or preterm births, our findings suggest a detrimental effect of the DDT exposure on fetal growth.** Neonatal anthropometric measures are considered as an important tool to detect newborns at higher risk of morbidity and impairment of growth. Efforts should be made to decrease exposure of women of reproductive age and to examine maternal DDT exposure in relation to long-term impact on health (Al-Saleh et al. 2012)

Title: Developmental defects of enamel in primary teeth and association with early life course events: A study of 6-36 month old children in Manyara, Tanzania (2013)

ABSTRACT: Background: Children with low birth weight show an increased prevalence of developmental defects of enamel in the primary dentition that subsequently may predispose to early childhood caries (ECC). Focusing 6-36 months old, the purpose of this study was to assess the frequency of enamel defects in the primary dentition and identify influences of early life course factors; socio-demographics, birth weight, child's early illness episodes and mothers' perceived size of the child at birth, whilst controlling for more recent life course

events in terms of current breastfeeding and oral hygiene. **Methods:** A cross-sectional study was conducted in the high fluoride area of Manyara, northern Tanzania including 1221 child-mother pairs who attended Reproductive and Child Health (RCH) clinics for immunization and/or growth monitoring. After the primary caregivers had completed face to face interviews at the health care facility, children underwent oral clinical examination whereby ECC and developmental defects of enamel were recorded using field criteria. All erupted teeth were examined and the enamel defects were assessed on buccal surfaces according to the modified DDE Index. **Results:** The prevalence of enamel defects was 33.3%. Diffuse opacities were the most common defects identified (23.1%), followed by hypoplasia (7.6%) and demarcated opacities (5.0%). The most frequently affected teeth were the upper central incisors (29.0% - 30.5%), whereas lower central incisors (4.3% to 4.5%) were least frequently affected. Multiple logistic regression analysis, adjusting for confounding the factors revealed that having normal birth weight (equal or more than 2500 g) associated with lower odds of having enamel hypoplasia [OR 0.2 (95% CI 0.1-0.7)]. No statistically significant association occurred between birth weight and diffuse opacities, demarcated opacities or combined DDE. **Conclusion:** Children with the history of low birth weight were more likely than their normal birth weight counterparts to present with enamel hypoplasia. In view of the frequent occurrence of enamel defects and the fact that hypoplasia may constitute a risk factor for future ECC, enamel defects should be included as a dental health indicator in epidemiological studies of children in northern Tanzania (Masumo et al. 2013).

Title: Increased enamel hypoplasia and very low birthweight infants (2013)

ABSTRACT: Birth cohort studies of developmental defects of enamel (DDE) and early childhood caries (ECC) in very low birthweight (VLBW) and normal birthweight (NBW) infants are rare. In this birth cohort of 234 VLBW and 234 NBW infants, we report the incidence of ECC and DDE at 8 and 18-20 mos of corrected age. Infant medical and maternal socio-demographic data were abstracted from medical records at birth. Dental assessments for ECC and DDE (enamel hypoplasia, demarcated and diffuse opacities) were completed at 8 and 18-20 mos. The incidence of hypoplasia was significantly higher in VLBW compared with NBW infants (8 mos, 19% vs. 2%; 18 mos, 31% vs. 8%). The incidence of ECC (International Caries Detection and Assessment System: ICDAS ≥ 2) was 1.4% (8 mos) and 12% (18-20 mos) and was similar between the VLBW and NBW groups. **At both ages, using a beta-binomial regression model to control for potential confounders (maternal and infant characteristics), we found increased risk for enamel hypoplasia among the VLBW infants compared with the NBW infants. African Americans had a lower risk for enamel hypoplasia at 18-20 mos. The VLBW infants should be monitored for ECC due to the presence of enamel hypoplasia (Nelson et al. 2013).**

Title: Organochlorine pesticide residues in maternal blood, cord blood, placenta, and breastmilk and their relation to birth size (2013)

ABSTRACT: There is a growing concern that persistent organic pollutants like organochlorine pesticides (OCPs) can impair fetal growth and affect birth size. However, currently available epidemiological evidence is inconclusive. In this case-control study, we examined the association between exposure to hexachlorocyclohexane (HCH) and its isomers (α -HCH, β -HCH and γ -HCH), dichlorodiphenyltrichloroethane (DDT) and

dichlorodiphenyldichloroethylene (DDE) and birth size. We recruited 60 infant-mother pairs, comprising of 30 term, small for gestational age babies with their mothers (Case group), and another 30 term, appropriate for gestational age babies with their mothers (Control group). This study was conducted in a tertiary hospital in Delhi, India, between March, 2009 and February 2010. Organochlorine pesticides were estimated in maternal blood, cord blood, placenta and breastmilk samples, using gas-liquid chromatography. Transplacental and transmammary transfer of OCPs was assessed by correlating the maternal blood OCP levels with those in cord blood and breastmilk by simple linear regression. The birthweight, crown heel length, head circumference, mid-arm circumference and ponderal index of the neonates was correlated with OCP levels in the maternal blood, cord blood, placenta and breastmilk. The OCP estimates were compared between samples of the case and control group. There was a significant ($P < 0.001$) transplacental transfer of all OCPs, however the transmammary transfer was insignificant for most OCPs except α -HCH. The OCP levels in the case group were higher than the control group; these were significantly more for t-HCH in cord blood and breastmilk; β -HCH in maternal blood, cord blood and breastmilk; DDE in placenta and DDT in breastmilk. There was a significant negative correlation between birthweight and t-HCH levels in maternal blood ($P = 0.022$), cord blood ($P < 0.001$), placenta ($P = 0.008$) and breastmilk ($P = 0.005$); β -HCH in cord blood ($P < 0.001$) and placenta ($P = 0.020$); γ -HCH in placenta ($P = 0.045$); and DDT ($P = 0.009$). Length at birth had a significant negative correlation with t-HCH in cord blood ($P = 0.014$) and breastmilk ($P < 0.001$); β -HCH in cord blood ($P = 0.016$) and breastmilk ($P = 0.012$); DDE in placenta ($P = 0.016$); and DDT in breastmilk ($P = 0.006$). Similarly, OCP levels were also found to be negatively correlated with head circumference, ponderal index and chest circumference in neonates. **We conclude that prenatal exposure to some OCPs could impair the anthropometric development of the fetus, reducing the birthweight, length, head circumference, chest circumference and ponderal index** (Dewan et al. 2013).

Title: A case control study of gene environmental interaction in fetal growth restriction with special reference to organochlorine pesticides (2012)

ABSTRACT: Objectives: Organochlorine pesticides (OCPs) and oxidative stress are reported to be associated with adverse reproductive outcomes. Glutathione S-transferase (GST) is a polymorphic supergene family involved in the detoxification of numerous toxins including OCPs. OCPs are endocrine disrupter and prenatal exposure to them may be associated with fetal growth restriction (FGR). The objectives of the present study were (i) to determine the frequencies of polymorphic alleles of GSTM1 and GSTT1 genes in women with idiopathic FGR, (ii) to analyze the maternal and cord blood levels of the OCPs, and (iii) to identify the gene environment interaction that increases the risk of FGR. Study design: Maternal and cord blood samples of 50 FGR cases (birth weight <10 percentile for gestational age as per Lubchenco's growth chart) and equal number of normal pregnancies who were occupationally non exposed to OCPs and excluding all the known high risk factors such as anemia, hypertension, antiphospholipid antibody syndrome, medical disease, dietary habit, living style, parity, and BMI. The collected samples at the time of delivery/after delivery were analyzed for OCPs levels by gas chromatography and polymorphic analysis for GSTM1/GSTT1 gene using multiplex PCR. Results: Significantly higher levels of α, β, γ -HCH and p,p'-DDT were found in maternal blood and significantly higher levels of β and γ -HCH and p,p'-DDT were found in cord blood of FGR cases as compared to controls. The genotypic distribution of GSTM1/GSTT1 was almost similar in both the groups, but the frequency of GSTM1-/GSTT1- (null) genotype was significantly higher in FGR cases as compared to

controls ($p < 0.05$, OR = 6.42). When interaction between GSTM1/GSTT1 genes polymorphism-OCPs levels and birth weight (gene-environment interaction) was ascertained, a significant association was seen between β -HCH and GSTM1- genotype with reduction in birth weight of 213 g. Conclusion: Higher levels of OCPs in pregnant women may be considered as an important aetiological factor in 'idiopathic' FGR. GST polymorphism can influence the relationship between prenatal exposure to pesticides and FGR. The present study provides evidence that polymorphism in xenobiotic metabolising genes may modify the effect of environmental health hazards and increase the risk of FGR (Sharma et al. 2012) (01).

Title: Fetal exposure to organochloride compounds and birth weight. Exposition foetale aux organochlorés et poids de naissance (2012)

Abstract: Associations between birth weight and fetal exposure to polychlorinated biphenyls (PCBs) and to dichlorodiphenyldichloroethylene (DDE) were examined in 12 European birth cohorts. **Exposure to PCBs, but not to DDE, appeared to be associated with lower birth weight** (Nicolle-Mir, L. 2012).

d) Childhood Growth

Summary: Available evidence is mixed but supports the possibility of an association between prenatal or early life exposures to DDE and reduced childhood or pubertal growth. In only one study were the results consistent for males and females.

Title: Prenatal exposure to the major DDT metabolite 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) and growth in boys from Mexico (2010)

ABSTRACT: Recent data suggest that prenatal exposure to p,p'-DDE may reduce height and increase body mass index (BMI) in childhood, thus potentially raising the risk of adult health problems. The association between prenatal DDE exposure and growth was evaluated in 788 boys from Chiapas, an area of Mexico where DDT was recently used. The median DDE levels in maternal serum at birth (2002-2003) were 2.7 γ g/g lipid. 2633 measurements of height (cm) and weight (kg) were obtained in 2004-2005. The median age of the children during follow-up was 18 months (quartiles 14 and 22 months). Height and body mass index (kg/m²) were age-standardized and expressed as standard deviation scores (SDS). Multivariate random-effect models for longitudinal data were fitted and predicted height and BMI SDS were estimated from the adjusted models. Overall, associations between prenatal DDE level and height or BMI SDS at any given age were not observed. For example, the predicted values showed that children with the highest exposure (DDE: $>9.00\gamma$ g/g) compared to those least exposed (DDE: $<3.01\gamma$ g/g) grew similarly and they had a BMI SDS similar to the reference group. **The results do not support the prior findings of an association of DDE exposure with childhood height or BMI** (Cupul-Uicab et al 2010).

Title: Prenatal organochlorine compound exposure, rapid weight gain, and overweight in infancy (2011)

ABSTRACT: Background: Although it has been hypothesized that fetal exposure to endocrine-disrupting chemicals may increase obesity risk, empirical data are limited, and it is uncertain how early in life any effects may begin. Objectives: We explored whether prenatal exposure to several organochlorine compounds (OCs) is associated with rapid growth in the first 6 months of life and body mass index (BMI) later in infancy. Methods: Data come from the INMA (Infancia y Medio-Ambiente) Child and Environment birth cohort in Spain, which recruited 657 women in early pregnancy. Rapid growth during the first 6 months was defined as a change in weight-for-age z-scores ≥ 0.67 , and elevated BMI at 14 months, as a z-score \geq the 85th percentile. Generalized linear models were used to estimate the risk of rapid growth or elevated BMI associated with 2,2-bis(p-chlorophenyl)-1,1-dichloroethylene (DDE), hexachlorobenzene, β -hexachlorohexane, and polychlorinated biphenyls in first-trimester maternal serum. Results: After multivariable adjustment including other OCs, DDE exposure above the first quartile was associated with doubling of the risk of rapid growth among children of normal-weight (BMI ≤ 25 kg/m²), but not overweight, mothers. DDE was also associated with elevated BMI at 14 months (relative risk per unit increase in log DDE = 1.50; 95% confidence interval, 1.11-2.03). Other OCs were not associated with rapid growth or elevated BMI after adjustment. Conclusions: **In this study we found prenatal DDE exposure to be associated with rapid weight gain in the first 6 months and elevated BMI later in infancy, among infants of normal-weight mothers. More research exploring the potential role of chemical exposures in early-onset obesity is needed** (Mendez et al. 2011).

Title: Serum concentrations of organochlorine pesticides and growth among Russian boys (2012)

ABSTRACT: Background: Limited human data suggest an association of organochlorine pesticides (OCPs) with adverse effects on children's growth. Objective: We evaluated the associations of OCPs with longitudinally assessed growth among peripubertal boys from a Russian cohort with high environmental OCP levels. Methods: A cohort of 499 boys enrolled in the Russian Children's Study between 2003 and 2005 at 8-9 years of age were followed prospectively for 4 years. At study entry, 350 boys had serum OCPs measured. Physical examinations were conducted at entry and annually. The longitudinal associations of serum OCPs with annual measurements of body mass index (BMI), height, and height velocity were examined by multivariate mixed-effects regression models for repeated measures, controlling for potential confounders. Results: Among the 350 boys with OCP measurements, median serum hexachlorobenzene (HCB), β -hexachlorocyclohexane (β HCH), and p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE) concentrations were 159 ng/g lipid, 168 ng/g lipid, and 287 ng/g lipid, respectively. Age-adjusted BMI and height z-scores generally fell within the normal range per World Health Organization standards at entry and during follow-up. However, in adjusted models, boys with higher serum HCB, β HCH, and p,p'-DDE had significantly lower mean [95% confidence interval (CI)] BMI z-scores, by -0.84 (-1.23, -0.46), -1.32 (-1.70, -0.95), and -1.37 (-1.75, -0.98), respectively, for the highest versus lowest quintile. In addition, the highest quintile of p,p'-DDE was associated with a significantly lower mean (95% CI) height z-score, by -0.69 (-1.00, -0.39) than that of the lowest quintile. Conclusions: **Serum OCP concentrations measured at 8-9 years of age were associated with reduced growth, particularly reduced BMI, during the peripubertal period, which may affect attainment of optimal adult body mass and height** (Burns et al. 2012).

Title: Prenatal dichlorodiphenyldichloroethylene (DDE) exposure and child growth during the first year of life (2012)

ABSTRACT: Background: Due to its long-term persistence in the environment and its ability to cross the placental barrier, prenatal p,p'-dichlorodiphenyldichloroethene (DDE) exposure continues to be a public health concern. This study aimed to evaluate the association between prenatal DDE exposure and child growth, at birth and during the first year of life. Methods: 253 pregnant women were recruited between January 2001 and June 2005 in a prospective cohort in Morelos, Mexico. Serum levels of DDE were measured during each trimester of pregnancy by gas chromatography with an electron capture detector. Using the generalized mixed-effects models, the association between DDE and child growth parameters (weight-for-age, length-for-age, weight-for-length, BMI-for-age and head circumference-for-age Z-scores) from birth to 1 year of age was assessed. Maternal dietary intake was considered as covariable among others. Results: DDE levels were 6.3 ± 2.8 ng/mL (first trimester), 6.6 ± 2.9 ng/mL (second trimester), and 7.6 ± 2.9 ng/mL (third trimester). After adjusting for potential confounder variables, **no significant associations were observed with prenatal DDE exposure and each of the selected parameters. Conclusions: Our results show no evidence of an association between prenatal DDE exposure and child growth during the first year of life** (Garced et al. 2012)

Title: Birth weight and prenatal exposure to polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE): A meta-analysis within 12 European birth cohorts (2012)

ABSTRACT: Objectives: Exposure to high concentrations of persistent organochlorines may cause fetal toxicity, but the evidence at low exposure levels is limited. Large studies with substantial exposure contrasts and appropriate exposure assessment are warranted. Within the framework of the EU (European Union) ENRIECO (Environmental Health Risks in European Birth Cohorts) and EU OBELIX (Obesogenic Endocrine disrupting chemicals: Linking prenatal exposure to the development of obesity later in life) projects, we examined the hypothesis that the combination of polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE) adversely affects birth weight. Methods: We used maternal and cord blood and breast milk samples of 7,990 women enrolled in 15 study populations from 12 European birth cohorts from 1990 through 2008. Using identical variable definitions, we performed for each cohort linear regression of birth weight on estimates of cord serum concentration of PCB-153 and p,p'-DDE adjusted for gestational age and apriori selected covariates. We obtained summary estimates by meta-analysis and performed analyses of interactions. Results: The median concentration of cord serum PCB-153 was 140ng/L (range of cohort medians 20-484ng/L) and that of p,p'-DDE was 528ng/L (range of cohort medians 50-1,208ng/L). Birth weight decreased with increasing cord serum concentration of PCB-153 after adjustment for potential confounders in 12 of 15 study populations. The meta-analysis including all cohorts indicated a birth weight decline of 150g [95% confidence interval (CI): -250, -50g] per 1- μ g/L increase in PCB-153, an exposure contrast that is close to the range of exposures across the cohorts. A 1- μ g/L increase in p,p'-DDE was associated with a 7-g decrease in birth weight (95% CI: -18, 4g). **Conclusions: The findings suggest that low-level exposure to PCB (or correlated exposures) impairs fetal growth, but that exposure to p,p'-DDE does not. The study adds to mounting evidence that low-level exposure to PCBs is inversely associated with fetal growth** (Govarts et al. 2012).

e) Age of Menarche and Pubertal Stages

Summary: Although results are mixed, there is no conclusive evidence that DDT or DDE is associated with change in age of menarche or pubertal stages.

Title: Internal exposure to pollutants and sexual maturation in Flemish adolescents (2011)

ABSTRACT: Flanders is densely populated with much industry and intensive farming. Sexual maturation of adolescents (aged 14-15 years) was studied in relation to internal exposure to pollutants. Serum levels of pollutants and sex hormones were measured in 1679 participants selected as a random sample of the adolescents residing in the study areas. Data on sexual development were obtained from the medical school examination files. Self-assessment questionnaires provided information on health, use of medication and lifestyle factors. In boys, serum levels of hexachlorobenzene (HCB), p,p'-DDE and polychlorinated biphenyls (sum of marker PCB138, 153 and 180) were significantly and positively associated with pubertal staging (pubic hair and genital development). Higher levels of serum HCB and blood lead were associated with, respectively, a lower and a higher risk of gynecomastia. In girls, significant and negative associations were detected between blood lead and pubic hair development; higher exposure to PCBs was significantly associated with a delay in timing of menarche. **Environmental exposures to pollutants at levels actually present in the Flemish population are associated with measurable effects on pubertal development. However, further understanding of toxic mode of action and sensitive windows of exposure is needed to explain the current findings** (Den Hond et al. 2011).

f) Developmental Neurotoxicity

Summary: The studies provide consistent evidence for perinatal exposure having neurocognitive effects on a population level (Table 12), particularly for DDT.¹ Two well-conducted prospective studies (Eskenazi et al., 2006; Ribas-Fito et al., 2006b) indicate that perinatal exposure to DDT at levels above 0.20 µg/l [approximately 0.032 µg/g lipid] (Ribas-Fito et al., 2006b) or resulting in a 10-fold increase in newborn serum DDT levels within the range of 0.002–33 µg/g lipid (Eskenazi et al., 2006) is associated with an adverse effect on neuro-development up to age 4. The evidence for DDE is mixed.

Title: Pesticide exposure and neurodevelopmental outcomes: Review of the epidemiologic and animal studies (2013)

ABSTRACT: Assessment of whether pesticide exposure is associated with neurodevelopmental outcomes in children can best be addressed with a systematic review of both the human and animal peer-reviewed literature. This review analyzed epidemiologic studies testing the hypothesis that exposure to pesticides during pregnancy and/or early childhood is associated with neurodevelopmental outcomes in children. Studies that directly queried pesticide exposure (e.g., via questionnaire or interview) or measured pesticide or metabolite levels in biological specimens from study participants (e.g., blood, urine, etc.) or their immediate environment (e.g., personal air monitoring, home dust samples, etc.) were eligible for inclusion. Consistency, strength of association, and dose response were key elements of the framework utilized for evaluating epidemiologic studies. As a whole, the epidemiologic studies did not strongly implicate any particular pesticide as being causally related to adverse neurodevelopmental outcomes in infants and children. A few associations were unique for a health outcome and specific pesticide, and alternative hypotheses could not

be ruled out. Our survey of the in vivo peer-reviewed published mammalian literature focused on effects of the specific active ingredient of pesticides on functional neurodevelopmental endpoints (i.e., behavior, neuropharmacology and neuropathology). In most cases, effects were noted at dose levels within the same order of magnitude or higher compared to the point of departure used for chronic risk assessments in the United States. **Thus, although the published animal studies may have characterized potential neurodevelopmental outcomes using endpoints not required by guideline studies, the effects were generally observed at or above effect levels measured in repeated-dose toxicology studies submitted to the U.S. Environmental Protection Agency (EPA).** Suggestions for improved exposure assessment in epidemiology studies and more effective and tiered approaches in animal testing are discussed (Burns et al. 2013).

Title: Fetal heart rate and motor activity associations with maternal organochlorine levels: results of an exploratory study (2013)

ABSTRACT: Contemporaneous associations between circulating maternal organochlorines (OCs) and measures of fetal heart rate and motor activity were evaluated. A panel of 47 OCs, including pesticides and polychlorinated biphenyls (PCBs), was analyzed from serum of 50 pregnant women at 36 weeks gestation. Data were empirically reduced into four factors and six individual compounds. All participants had detectable concentrations of at least one-quarter of the assayed OCs and, in general, higher socioeconomic level was associated with higher OC concentrations. Fetal heart rate measures were not consistently associated with maternal OCs. **In contrast, one or more indicators of greater fetal motor activity were significantly associated with higher levels of the DDT and low chlorinated OC factors and five of the six individual compounds (heptachlor epoxide, trans nonachlor, oxychlordane, and PCBs 18 and 52).** This preliminary demonstration of associations between fetal motor activity and maternal concentrations of persistent and pervasive environmental contaminants suggests that fetal assessment may be useful in ascertaining the potential early effects of these compounds on development (DiPietro et al. 2013).

Title: Association of selected persistent organic pollutants in the placenta with the risk of neural tube defects (2011)

ABSTRACT: Persistent organic pollutants (POPs) have been associated with a wide range of adverse health effects. Our case-control study was performed to explore the association between placental levels of selected POPs and risks for neural tube defects (NTDs) in a Chinese population with a high prevalence of NTDs. Cases included 80 fetuses or newborns with NTDs, whereas the controls were 50 healthy, nonmalformed newborn infants. Placental concentrations of polycyclic aromatic hydrocarbons (PAHs), organochlorine pesticides, polychlorinated biphenyls, and polybrominated diphenyl ethers were analyzed by gas chromatography-mass spectrometry. The medians of PAHs, o,p'-isomers of dichlorodiphenyltrichloroethane (DDT) and metabolites, α - and γ -hexachlorocyclohexane (HCH), and α -endosulfan were significantly higher in case placentas than in controls. PAH concentrations above the median were associated with a 4.52-fold [95% confidence interval (CI), 2.10-9.74) increased risk for any NTDs, and 5.84- (95% CI, 2.28-14.96) and 3.71-fold

(95% CI, 1.57-8.79) increased risks for anencephaly and spina bifida, respectively. A dose-response relationship was observed between PAH levels and the risk of NTDs, with odds ratios for the second, third, and fourth quartiles, compared with the first, of 1.77- (95% CI, 0.66-4.76), 3.83- (95% CI, 1.37-10.75), and 11.67-fold (95% CI, 3.28-41.49), respectively. A dose-response relationship was observed for anencephaly and spina bifida subtypes. Similar results were observed for o,p'-DDT and metabolites, α -HCH, γ -HCH, and α -endosulfan, whereas no dose-response relationship was observed for the last two pollutants. **Elevated placental concentrations of PAHs, o,p'-DDT and metabolites, and α -HCH were associated with increased risks of NTDs in this population** (Ren et al. 2011).

g) Developmental Immunotoxicity

Summary: Studies of developmental immunotoxicity were inconclusive.

h) Effects on Male Reproductive Tract

Hypospadias

Summary: Human evidence is inadequate to conclude whether there is an association between exposure to DDT/DDE and hypospadias.

Title: Polymorphism in CYP1A1, GSTM1, GSTT1 genes and organochlorine pesticides in the etiology of hypospadias (2011)

ABSTRACT: Exposure to endocrine-disrupting chemicals (EDCs) and maternal endogenous estrogen may cause hypospadias, common congenital anomaly. Several organochlorine pesticides (OCPs) have been reported to possess an endocrine-disrupting potential. Cytochrome P4501A1 (CYP1A1) and glutathione S-transferases (GSTM1 and GSTT1) of xenobiotic metabolizing enzyme family are involved in the metabolism of various environmental toxicants and steroidal hormones. Hence, the present study was designed to evaluate the role of CYP1A1, GSTM1, GSTT1 genes polymorphism, OCPs levels and risk of hypospadias. A total of 80 hypospadiac and 120 age-matched control boys were included. OCP levels in blood were determined using Gas Chromatograph equipped with electron capture detector (GC-ECD) and polymorphism in CYP1A1, GSTM1 and GSTT1 genes was evaluated by RFLP and multiplex PCR method. We observed significant high levels of β -hexachlorohexane (HCH), γ -HCH, and p,p'-dichlorodiphenyl- dichloroethylene (p,p'-DDE) in the cases. CYP1A1 polymorphisms were not significantly different among cases and controls, whereas concomitant deletion of GSTM1 and GSTT1 genotypes was significantly higher in cases as compared to controls. However, after adjusting for low birth weight and maternal occupational exposure, the results did not remain significant but odds of risk was higher (OR = 1.72, p = 0.14) among cases. **In conclusion, our study suggests irrespective of genetic predisposition, higher level of some OCPs may be associated with increased risk of hypospadias** (Shekharyadav et al.2011).

Title: A Nested Case-Control Study of Intrauterine Exposure to Persistent Organochlorine Pollutants and the Risk of Hypospadias (2012)

ABSTRACT: Background: Environmental exposures to endocrine disrupting chemicals have been suggested as a risk factor for male genital abnormalities such as hypospadias. The aim of

this case-control study was to investigate the association between fetal exposure to persistent organochlorine pollutants (POP) and the risk for hypospadias. Methodology/Principal Findings: The Southern Sweden Maternity Cohort (SSMC) contains serum samples collected in early pregnancy among women in Southern Sweden. Linkages with the Medical Birth Register, the Malformation Register and the In-patient Register resulted in 390 SSMC mothers who had given birth to a boy with hypospadias in year 1986-2002 (mean 1995). For 237 of these (cases) sufficient amounts of serum for the chemical analyses were available. For each case, a control boy from the SSMC was randomly selected, matched for maternal age, birth year, parity and maternal smoking. PCB-153, p,p'-DDE and hexachlorbenzene (HCB) were used as biomarkers for POP exposure. The exposures were categorized into quartiles based on the distributions among the controls. There were no statistically significant trends between the a priori categorisation of the exposure variables and the risk for hypospadias. However, when the upper HCB quartile (>26 ng/ml) was compared to the other quartiles an odds ratio of 1.65 (95% CI 1.02 to 2.69) was obtained. p,p'-DDE levels above median (>1.0 ng/ml) compared to levels below 0.1 ng/ml gave an OR of 1.69 (95% CI 0.97 to 2.93). Conclusions: **The present study suggests that fetal exposure to HCB and p,p'-DDE may be a risk factor for hypospadias** (Rignell-Hydbom, A., C. H. Lindh, et al. 2012).

Anogenital Distance

Summary: Two well-conducted epidemiological studies gave conflicting results for DDE exposure and anogenital distance.

Cryptorchidism

Summary: Four human studies did not show significant association between DDT/DDE and cryptorchidism.

Title: Prenatal exposure to organochlorine pesticides and cryptorchidism [Exposición prenatal a los plaguicidas organoclorados y criptorquidia] (2010)

ABSTRACT: The objective of this article is to determine the levels of organochlorine pesticides (HCB, β -HCH, pp'DDT, op'DDT and pp'DDE) in the serum lipids of mothers of newborns with cryptorchidism and compare the levels to a control group of mothers of newborns with descended testicles. The cases were composed of newborns with cryptorchidism (n=41), and the controls (n=41) newborns with descended testicles. Blood samples from both groups of mothers were used to determine the organochlorine pesticide levels. Cryptorchidism was diagnosed at birth by a neonatologist. The results showed that the organochlorine pesticide residues were found in the serum lipids of both groups of mothers. The median serum lipid levels (mg/kg-1 lipid- based) were statistically higher for the metabolites pp'DDT (0.464 vs. 0.269) and β -HCH (0.263 vs. 0.192) in the cryptorchidism group compared to the control group (p<0.01). **It could be concluded that the levels of the metabolites pp'DDT and β -HCH are higher among mothers of newborns with cryptorchidism. It is possible that substances with anti-androgenic effects could produce endocrine disruption, such as cryptorchidism, during fetal development** (Montes et al. 2010).

Urogenital Births Defects (UGBDs)

Title: High prevalence of micropenis in 2710 male newborns from an intensive-use pesticide area of Northeastern Brazil (2012)

ABSTRACT: Exposure to endocrine-disrupting chemicals (EDCs) has been suggested to contribute to the increasing trends of external genital malformation in male newborns. In Northeastern Brazil, the poor sanitary conditions found in the favelas encourage the widespread use of pesticides. This 2-year study of a total birth cohort of full-term male newborns in the regional hospitals of Campina Grande (Paraíba, Brazil) sought to (1) accurately establish for the first time the incidences of neonatal male genital malformations, (2) investigate the endocrine and genetic aetiologies of these malformations, and (3) evaluate their associations with possible prenatal exposure to EDCs. A total of 2710 male newborns were explored for cryptorchidism, hypospadias and micropenis. Cases were referred to the Pediatric Endocrine Clinic for endocrine and genetic investigations, and all parents were interviewed about their environmental/occupational exposure to EDCs before/during pregnancy by paediatric endocrinologists using a detailed questionnaire. We observed 56 cases of genital malformation (2.07%), including 23 cryptorchidism (0.85%), 15 hypospadias (0.55%), and 18 micropenis (0.66%). All cases exhibited normal/subnormal testosterone production and none presented androgen receptor or 5 α -reductase gene mutation. More than 92% of these newborns presented foetal contamination by EDCs, as their mothers reported daily domestic use of pesticides (i.e., DDT) and other EDCs. Most of these undervirilized male newborns presented additional EDC contamination, as 80.36% of the mothers and 58.63% of the fathers reported paid or unpaid work that entailed the use of pesticides and other EDCs before/during pregnancy for the mothers and around the time of fertilization for the fathers. **The high rate of micropenis in our population associated with an elevated percentage of parental environmental/occupational exposure to EDCs before/during pregnancy indicates that foetal contamination may be a risk factor for the development of male external genital malformation** (Gaspari et al. 2012).

i) Infant lower respiratory tract infections (LRTIs)

Title: Pre-natal exposure to dichlorodiphenyldichloroethylene and infant lower respiratory tract infections and wheeze (2012)

ABSTRACT: The aim of our study was to examine whether pre-natal exposure to dichlorodiphenyldichloroethylene (DDE) increases the risk of lower respiratory tract infections (LRTIs) and wheeze in infants. The study is based on a birth cohort of 1,455 mother-child pairs. Maternal serum concentrations of DDE, polychlorinated biphenyls (PCBs) and hexachlorobenzene (HCB) were measured during pregnancy. Parental reports on LRTI and wheeze were obtained when children were 12-14 months old. 35.4% of children developed at least one LRTI episode and 33.6% at least one wheezing episode during their first 12-14 months of life. Median DDE, PCBs and HCB concentrations were 116.3, 113.7 and 46.4 ng·g(-1) lipid, respectively. DDE concentrations were associated with LRTI risk (relative risk (RR) per 10% increase 1.11, 95% CI 1.00-1.22), also after adjustment for PCBs and HCB. In all quartiles of DDE exposure, the risk of LRTI was increased compared with the lowest quartile, but the increase was statistically significant only in the third quartile (RR 1.33, 95% CI 1.08-1.62). No association was observed for PCBs and HCB. Results were similar for wheeze. **This study suggests that pre-natal DDE exposure is associated with a**

higher risk of LRTI and wheeze in infants independently of exposure to other organochlorine compounds (Gascon et al. 2012)

j) Prenatal exposure and hypertension

Title: Prenatal exposure to the pesticide DDT and hypertension diagnosed in women before age 50: A longitudinal birth cohort study (2013)

ABSTRACT: Background: Elevated levels of the pesticide DDT (dichlorodiphenyl-trichloroethane) have been positively associated with blood pressure and hypertension in studies among adults. Accumulating epidemiologic and toxicologic evidence suggests that hypertension during adulthood may also be affected by earlier life and possibly the prenatal environment. Objectives: We assessed whether prenatal exposure to the pesticide DDT increases risk of adult hypertension. Methods: We examined concentrations of DDT (p,p'- and o,p'-) and its metabolite p,p'-DDE (dichlorodiphenyldichloroethylene) in prenatal serum samples from a subset of women (n = 527) who had participated in the prospective Child Health and Development Studies birth cohort in the San Francisco Bay area while they were pregnant between 1959 and 1967. We surveyed daughters 39-47 years of age by telephone interview from 2005 to 2008 to obtain information on self-reported physician-diagnosed hypertension and use of hypertensive medication. We used multivariable regression analysis of time to hypertension based on the Cox proportional hazards model to estimate relative rates for the association between prenatal DDT exposures and hypertension treated with medication in adulthood, with adjustment for potential confounding by maternal, early-life, and adult exposures. Results: Prenatal p,p'-DDT exposure was associated with hypertension [adjusted hazard ratio (aHR) = 3.6; 95% CI: 1.8, 7.2 and aHR = 2.5; 95% CI: 1.2, 5.3 for middle and high tertiles of p,p'-DDT relative to the lowest tertile, respectively]. These associations between p,p'-DDT and hypertension were robust to adjustment for independent hypertension risk factors as well as sensitivity analyses. **Conclusions: These findings suggest that the association between DDT exposure and hypertension may have its origins early in development** (La Merrill et al. 2013).

11. HAZARD CHARACTERIZATION

11.1 Summary of hazard identification for use in hazard characterization

11.2 Dose-response assessment

11.2.1 Methods used for dose-response assessment

11.2.2 Non-cancer effects

11.2.2.1 Experimental animal studies

11.2.2.2 Human studies

11.2.3 Carcinogenicity

11.2.3.1 Experimental animal studies

11.2.3.2 Human studies

12. EXPOSURE ASSESSMENT

12.1 Introduction

12.2 DDT application by spray operators

12.3 Generic model for occupational and residential exposure

12.4 Occupational exposure

12.4.1 Adipose tissue

12.4.2 Blood

12.5 Residents in sprayed areas

12.5.1 Known residents of sprayed houses

12.5.2 General population living in areas using indoor residual spraying

12.6 Summary of adult occupational and residential exposure

12.7 Breast milk

Title: Assessment of organochlorine pesticides in human milk and risk exposure to infants from North-East India (2011)

ABSTRACT: Despite the worldwide ban on use of persistent organochlorine pesticides, their usage continued until recently in India, for vector-borne disease eradication programs and agricultural purposes. The concentrations of organochlorine contaminants, DDT and HCH, have been determined in human breast milk from Dibrugarh and Nagaon districts of Assam state, North-East India. The results demonstrated that the mean levels of total DDT were 3210 ng/g lipid wt. and 2870 ng/g lipid wt. and total HCH were 2720 ng/g lipid wt. and 2330 ng/g lipid wt. in Nagaon and Dibrugarh respectively. There was no significant difference in the levels of investigated pollutants between the two districts. Significant differences in ADI (Average daily intake) for total DDT were found between the two districts. In addition, a positive correlation was observed between OCP levels in breast milk and age of mothers. Based on OCP levels in human breast milk, the ADI by the infants has been estimated. **It has been found that high daily intake of DDTs and HCHs by the infants exceeded the TDI (Tolerable daily intake) which implied that infants of the region are potentially at high risk by these contaminants (Mishra and Sharma 2011).**

Title: Pesticide residues in human breast milk: Risk assessment for infants from Punjab, India (2013)

ABSTRACT: Punjab state in India is an agrarian society, where agriculture is the lifeline of farming community. To keep pace with increasing demands of food for growing population the indiscriminate use of pesticides has led to the contamination of environment and food commodities in this region. Analysis of human breast milk samples (n=53) for pesticide residues revealed the presence of β -, γ -HCH, p,p' DDD, p,p' DDE, p,p' DDT and endrin with mean concentration of 97.9, 101.7, 239.8, 1574.1, 100.3 and 90.7 ng-g⁻¹ lipid wt., respectively. In addition, occurrence of β -endosulfan, endosulfan sulphate, cypermethrin and chlorpyrifos in this study have also been reported for the first time in human breast milk in Punjab, India. With increase in parity, HCH and DDT residue burden in donor's milk decreased. **Although levels of HCH and DDT residues in breast milk samples have decreased significantly, yet estimated daily intake values for DDT are higher than the FAO/WHO permissible tolerable daily intake values for few infants (Bedi et al. 2013).**

Title: Levels of Organohalogenated Pollutants in Human Milk Samples from Konya City, Turkey (2011)

This study reports the levels of organochlorine pesticides (OCPs, α -, β -, γ - and Δ -HCHs, p,p'-DDE, p,p'-DDD and p,p'-DDT), polychlorinated biphenyls (PCBs, PCB 28, 52, 101, 153, 138 and 180 congeners) and polybrominated diphenyl ethers (PBDEs, PBDE 47, 99, 100, 153 and 154 congeners) in 45 individual human milk samples collected from Konya City, Turkey. Average concentrations of Σ HCHs, Σ DDTs, Σ PCBs and Σ PBDEs were 22.62, 37.10, 104.95 and 67.34 ng/g lipid wt., respectively. No significant differences in investigated pollutants were found between primiparous and multiparous mothers. There was no correlation between levels of each group of pollutants in human milk and the age of mothers. Moreover, there was no significant difference in the levels of Σ DDTs, between mothers who have eaten fish more than once a week and those who consumed fish less than once. An analysis of the infant exposure to DDTs, HCHs and PCBs via mother's milk indicated that the estimated daily intakes of these pollutants were below the guideline proposed by the World Health Organization (WHO) and the Health Canada which means that there is definitely no concern on children health. **The results indicated that the daily infant intakes of DDTs, HCHs and PCBs via mother's milk, collected from Konya City, Turkey, were below the World Health Organization and the Health Canada guidelines (Ozcan et al. 2011)**

Title: Polybrominated diphenyl ethers, polychlorinated biphenyls and organochlorine pesticides in human milk as markers of environmental exposure to these compounds (2011)

ABSTRACT: This study aimed at the generation of preliminary results allowing for the assessment of breastfed infants exposure to polybrominated diphenyl ethers (PBDEs) which constitute important contaminants in places of human habitation. The second goal was to compare the concentrations of these compounds with other contaminants which people are exposed to via food chain. 28 breast milk samples from women living in Warsaw and neighbourhood were analyzed for polybrominated diphenyl ethers (BDE-47, BDE-99, BDE-

153), polychlorinated biphenyls (CB-77, CB-101, CB-118, CB-126, CB- 138, CB-153, CB170, CB-180) and organochlorine pesticides (HCB, β -HCH, γ -HCH, p,p'-DDE, p,p'-DDD, p,p'-DDT). **The Σ DDT levels noted in our studies were higher than in other European countries.** The concentrations of the examined polychlorinated biphenyls and polybrominated diphenyl ethers did not diverge from the levels presented by other authors and are comparable to the levels noted in other countries in Europe (Hernik et al. 2011).

Title: Polychlorinated biphenyl and organochlorine pesticide levels in human breast Milk from the mediterranean city Antalya, Turkey (2011)

ABSTRACT: In this study, organochlorine pesticides (OCPs) and polychlorinated biphenyles (PCBs) levels were determined in 100 human milk samples from the city of Antalya. The levels of seven major PCB congeners; 28, 52, 101, 118, 138, 153, 180 and nine OCPs, α -HCH, β -HCH, γ -HCH, HCB, heptachlor epoxide, p,p'-DDT, p,p'-DDE, endosulfan- α and endosulfan- β were determined by gas chromatography with ECD detection. The levels of analyzed compounds were as follows: Σ PCBs 27.46 ± 11.58 , Σ DDT $1,407 \pm 123$, and Σ BHC 160 ± 490 ng/g lipid wt.basis. **PCB 153 and p,p'-DDE were the dominant contaminants. The results have been discussed and compared with similar studies from other regions of Turkey (Cok et al. 2011).**

Title: Occurrence and levels of organochlorine compounds in human breast milk in Bangladesh (2012)

ABSTRACT: In low-income countries, the use of some organochlorine pesticides is still common in order to increase food production. Monitoring the chemical exposure is an important step in risk-reducing strategies. This is the first study to report concentrations of organochlorines in breast milk of women from Bangladesh where farming is the main income source. Organochlorines such as p, p'-DDT, o, p'-DDT, p, p' -DDE, p, p' -DDD (i.e., Σ DDT), HCB, α -, β - and γ -HCH, trans-chlordane, cis-chlordane, oxy-chlordane, trans-nonachlor, cis-nonachlor, mirex and polychlorinated biphenyls (CB 28, 52, 99, 101, 105, 114, 118, 123, 128, 138, 141, 149, 153, 156, 157, 163, 167, 170, 180, 183, 187, 189, 194) were analyzed in breast milk collected in 2002 from 72 first-time mothers (median age 20. years) living in the rural area Matlab, Bangladesh. While the concentrations of PCBs and many of the pesticides were low, the concentrations of p,p'-DDT and its metabolite p,p'-DDE were high (median 349 and 1645 ngg⁻¹ lipid, respectively) in comparison to other countries. The median value of Σ DDT was 2123 ngg⁻¹ lipid. The estimated daily exposure to p,p'-DDT, p,p'-DDE and Σ DDTs was 10, 30 and 42 μ gkg⁻¹ body weight, respectively, in 3 months old infants. The p,p'-DDE/p,p'-DDT ratio ranged from 1 to 23, where 58% of the mothers had a ratio below 5 indicating recent or ongoing DDT exposure. **This study reports infant exposure and maternal body burden of organochlorines through breast milk. Although the findings give no reason to limit breast-feeding, it is essential to identify the main exposure sources and find means to decrease the exposure (Bergkvist et al. 2012).**

Title: High levels of DDT in breast milk: Intake, risk, lactation duration, and involvement of gender (2012)

ABSTRACT: We investigated presence and levels of DDT in 163 breast milk samples from four South African villages where, in three of them, malaria is controlled with DDT-sprayed indoors. Mean Σ DDT levels in breast milk were 18, 11, and 9.5 mg/kg mf (milk fat) from the three DDT-sprayed villages, respectively, including the highest Σ DDT level ever reported for breast milk from South Africa (140 mg/kg mf). Understanding the causes for these differences would be informative for exposure reduction intervention. The Provisional Tolerable Daily Intake (PTDI) for DDT by infants, and the Maximum Residue Limit (MRL) were significantly exceeded. DDT had no effect on duration of lactation. **There were indications (not significant) from DDT-sprayed villages that first-born female infants drink milk with more Σ DDT than first-born male infants, and vice versa for multipara male and female infants, suggesting gender involvement on levels of DDT in breast milk - requiring further investigation** (Bouwman et al. 2012).

Title: Analysis of organochlorine pesticide residues in human and cow's milk in the towns of Asendabo, Serbo and Jimma in South-Western Ethiopia (2012)

ABSTRACT: The level of some OCPs in human and cow milk collected from Asendabo, Serbo and Jimma in South-West Ethiopia were analyzed using GC-ECD. Results of the analysis indicated that all samples contained detectable quantities of p,p'-DDT and its metabolites, p,p'-DDE and p,p'-DDD, but none of the other OCPs analyzed. Mean levels of total DDT in the human and cow milk samples in the three areas were 12.68 and 0.389 $\mu\text{g kg}^{-1}$ respectively. The distributions of p,p'-DDT, p,p'-DDE and p,p'-DDD in the human milk samples from the three locations followed the same trend in which the proportion of p,p'-DDT was the highest in all the three cases, comprising 55-71% of total DDT, followed by p,p'-DDE, 26-39%, and the least, p,p'-DDD of 2-5%. The mean ratio of DDT/DDE concentration for the three areas was calculated to be 2.01. This value was much higher than the values reported from other countries in earlier studies and indicates the existence of a higher quantity of DDT from a fresh input in the three study areas. **The mean estimated daily intake of DDT by infants from mother's milk in the three locations was found to be 62.17 $\mu\text{g kg}^{-1}$ body weight, which is about three times higher than the acceptable daily intake set by WHO/FAO for total DDT, 20 $\mu\text{g kg}^{-1}$ of body weight. This alarmingly high daily intake value is a cause for concern, since children are highly susceptible to effects from such environmental contaminants. The study has revealed that people in the study areas are facing exposure to DDT from recent use. The observed contamination of mother's milk and the possible transfer of the contaminant from mother to child is an obvious risk associated with breast-feeding in the study areas and possibly in other parts of the country too** (Gebremichael, Birhanu and Tessema 2012).

Title: Organochlorine compounds, nitro musks and perfluorinated substances in breast milk - Results from Bavarian monitoring of breast milk 2007/8 (2013)

ABSTRACT: The aim of the Bavarian Monitoring of Breast Milk (BAMBI) project was to examine 10 organochlorine pesticides (OPs), 3 nitro musks, 6 indicator polychlorinated biphenyls (PCBs), 7 polychlorinated dibenzo-p-dioxins (PCDDs), 10 polychlorinated dibenzofurans (PCDFs), 12 dioxin-like PCBs (dl-PCBs) and several perfluorinated alkyl compounds in breast milk samples. A total of 516 breast milk samples were collected from seven regions in Bavaria and were analyzed by means of GC/ECD, GC/HRMS, and LC/MS-MS. **Concerning the OPs, only hexachlorobenzene and a metabolite of DDT, 1,1-dichloro-2,2-bis(4-chlorophenyl) ethylene (p,p'-DDE), could be quantified in all samples (median: 16ngg-1 lipid and 63ngg-1 lipid, respectively).** Median concentrations of 150ngg-1 lipid (range: 3-1900ngg-1 lipid) were found for the sum of the indicator PCBs. The concentrations of the PCDDs/PCDFs and the dl-PCBs ranged from 0.8 to 15.1 (median 5.7) pg WHO-TEQ1998g-1 lipid and from 1.5 to 18.9pg (median 6.4) WHO-TEQ1998g-1 lipid, respectively. The median perfluorooctane sulfonate concentration was 0.05µgL-1 (range: <0.02-0.26µgL), while the other PFCs were observed only in a subset of samples. On the basis of the median and 95th percentile concentration, "medium" and "high" intake levels were estimated for a 3-month-old exclusively breastfed infant. In particular, "medium" and "high" intake levels were calculated of 69 and 133pg WHO1998 TEQkg-1 b.w. for PCDDs/PCDFs, 8 and 21ngkg-1 b.w. for dl-PCBs, and 6 and 25ngkg-1 b.w. for perfluorooctane sulfonate, respectively. The calculated intake for perfluorinated substances is clearly below the tolerable daily intake (TDI), while the established TDI values are still clearly exceeded for PCDDs/PCDFs and dl-PCBs (Raab et al. 2013)

Title: Presence of organochlorine pesticides in breast milk samples from Colombian women (2013)

ABSTRACT: The presence of Organochlorine Pesticides (OCPs) in biological and environmental samples has been studied for decades in many countries. Nonetheless, studies in Latin American countries like Colombia have been scarce. Determining the presence of OCPs in breast milk will be of relevance to assess exposures, potential health risks, and for surveillance among Latin American populations. Thirty-two breast-feeding mothers were selected to voluntarily participate in the study. Breast milk samples were analyzed for 10 OCPs (α -, β -, γ -, δ -HCH, Heptachlor, α -, γ -Chlordane, 4,4' DDT, 4,4' DDE, 4,4' DDD). Milk samples were analyzed using liquid-liquid extraction, followed by sulfuric acid clean-up, and quantified using GC/ μ ECD. Results were confirmed by GC/MS. OCPs concentrations were normalized using fat content. **In all but one sample, 4,4' DDE was quantified in concentrations ranging between<17 and 14948ngg-1 (ng of OCP per g of lipids), with a mean value of 203ngg-1.** One woman had 4,4' DDE concentrations that were orders of magnitude above the average concentrations observed worldwide. Concentrations of 4,4' DDE in a second breast milk sample collected in a different time period of lactation from a subgroup of 13 women from the original participants, showed no statistically significant difference with the concentrations found in the first sample. **Based on the results obtained from the Persistent Organic Pollutants Global Monitoring Plan report of 2009 of the Stockholm Convention, Colombia ranks fourth from bottom to top in terms of 4,4' DDE average concentrations** (Rojas-Squella et al. 2013).

Title: Human milk POPs and neonatal risk trend from 1982 to 2009 in the same geographic region in Serbia (2013)

ABSTRACT: Three groups of POPs - DDT, HCH and PCBs were monitored in early human milk for 27. years (1982-2009), as a measure of environmental pollution in the same geographic region (South Bačka, Vojvodina, Serbia). Measurements were performed using ECD GC Varian 3400. Concentrations of DDT and HCH had general decreasing trend from 1982 to 2009. However, the concentrations of both groups of compounds showed small rises in 1994. Concentrations of PCBs had general decreasing trend from 1982 to 2009 - smooth and steep only till 1994 and with two small peaks in 2003 and 2009. The latest estimated daily intake of DDT and HCH was well below the EU upper limit for pesticides in food intended for infants and small children. Although the estimated daily intake of PCBs was far below the upper limit for daily milk products in Serbia, its increase in 2003 and 2009 is a clear indication of environmental influx of these compounds after the 1994 measurements. The likely explanation for such POP profiles in South Bačka could have been a series of negative environmental impacts escalating in 1999, after which four hot spots were identified in Serbia (Novi Sad, Pančevo, Bor and Kragujevac) by UNEP. **The results of this monitoring showed that although a long standing environmental presence of POPs has a decreasing trend, their occasional output in the environment may cause bioaccumulation and biomagnification in human organisms which already start in the neonatal age through mother-child transfer via human milk (Vukavić et al. 2013).**

12.7.1 Blood serum

Title: Environmental exposure to POPs and heavy metals in urban children from Dhaka, Bangladesh (2011)

ABSTRACT: Persistent organic pollutants (POPs) and heavy metals are well known environmental pollutants. Even though numerous studies have been carried out to assess human exposures to these compounds, there is still a lack of data on humans from developing countries, especially in underprivileged children. The objective of this study was to assess the exposure to POPs and heavy metals in children from Dhaka, Bangladesh. One specific aim was to investigate whether children working at, or living close to, open waste disposal sites (WDSs) were more heavily exposed than other urban children. In 2008, blood and serum were collected from 73 children aged 7-16 from five neighbourhoods. Some of the children lived and worked at WDSs (N = 31), others lived next to a WDS (N = 17), whereas some children lived far from such sites (N = 25). Blood levels of lead (B-Pb), cadmium (B-Cd), and selenium (B-Se) were determined by ICP-MS for all subjects. The metal levels were high, with B-Pb overall mean 120 µg L⁻¹ (range 40-220), B-Cd 0.74 µg L⁻¹ (0.22-4.1), and B-Se 120 µg L⁻¹ (81-170). There were no marked differences between children from the different neighbourhoods, or between WDS workers and other children. PCB levels were low and with no contrast between neighbourhoods, for CB-153 the overall mean was 7.0 ng g⁻¹ fat (2.8-51). In contrast, high levels of DDTs were observed in all children, for 4,4'-DDE 1300 ng g⁻¹ fat (420-4600), and for 4,4'-DDT 326 ng g⁻¹ fat (44-1400), indicating ongoing exposure. PBDE levels were low, and BDE-209 was quantitated mainly in children working at or living close to WDSs. **In conclusion, the high levels of DDTs, lead and cadmium observed in children from Dhaka are of concern (Linderholm et al. 2011).**

Title: Exposure to chemical mixtures in Mexican children: high-risk scenarios (2012)

ABSTRACT: In developing countries, the management of environmental toxicants is inadequate, thus, humans may be exposed to levels higher than normal levels (background levels). Therefore, the aim of this study was to evaluate the exposure level of Mexican children to dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE), lead, and polycyclic aromatic hydrocarbons [using 1-hydroxypyrene (1-OHP) as exposure biomarker] and to assess the percentage of children exposed to these four compounds at concentrations higher than normal in each community studied. We performed random sampling in eight communities in Mexico (five communities in Chiapas State and three communities in San Luis Potosi State). DDT and DDE were analyzed by gas chromatography/mass spectrometry, the quantification of lead in blood was performed using atomic absorption spectrophotometry, and 1-OHP analyses were performed using HPLC with a fluorescence detector. Elevated DDT, DDE, and 1-OHP levels were found in children living in the indigenous communities of Chiapas State, while higher blood lead levels were found in two communities in San Luis Potosí. Approximately 30 % of children living in Chiapas were exposed to all four compounds at concentrations above the guidelines for each compound, whereas 48 % of children studied were exposed to all four contaminants at concentrations higher than normal in a community in San Luis Potosí State. **As expected, our results showed that in hot spots, children are exposed to levels higher than normal. Therefore, child environmental health programs are urgently needed** (Dominguez-Cortinas et al. 2012)

Title: Exposure assessment of organochlorine pesticides, arsenic, and lead in children from the major agricultural areas in Sonora, Mexico (2013)

ABSTRACT: There is a lack of information of exposure to organochlorine pesticides (OCP) and some metals, such as lead (Pb) and arsenic (As), both of which were used as arsenicals pesticides, in children living in the major agricultural areas of Mexico. The objective of this study was to assess the exposure of children to different OCP, As, and Pb in the Yaqui and Mayo valleys of Sonora to generate population baseline levels of these toxins. A cross-sectional study was undertaken in 165 children (age 6-12 years old) from 10 communities from both valleys during 2009. Blood samples were analyzed for OCP and Pb and first morning void urine for inorganic As (InAs). **All of the blood samples had detectable levels of dichlorodiphenyltrichloroethylene (p,p'-DDE) ranging from 0.25 to 10.3 µg/L. However lindane, dichlorodiphenyltrichloroethane (p,p'-DDT), aldrin, and endosulfan were detected in far less of the population (36.4, 23.6, 9.1, and 3 %, respectively).** Methoxychlor and endrin were not found in any sample. The average value of Pb in this population was 3.2 µg Pb/dL (range 0.17-9.0) with 8.5 % of the samples having levels <5.0 µg Pb/dL. Urinary As levels ranged from 5.4 to 199 µg As/L with an average value of 31.0 µg As/L. Levels > 50 µg/L were observed in 12.7 % of the samples. **Our results show that is important to start a risk-reduction program to decrease exposure to these toxins in Mexican communities. In addition, the results can be used to establish the baseline levels of exposure to these toxins in this agricultural region and may be used as a reference point for regulatory agencies** (Meza-Montenegro et al. 2013).

Title: Levels of selected persistent organic pollutants in blood from delivering women in seven selected areas of São Paulo State, Brazil

ABSTRACT: Persistent organic pollutants (POPs) present in the living environment are thought to have detrimental health effects on the population, with pregnant women and the developing foetus being at highest risk. We report on the levels of selected POPs in maternal blood of 155 delivering women residing in seven regions within the São Paulo State, Brazil. The following selected POPs were measured in the maternal whole blood: 12 polychlorinated biphenyls (PCBs) congeners (IUPAC Nos. 99, 101, 118, 138, 153, 156, 163, 170, 180, 183, 187, 194); dichlordiphenyltrichloroethane p,p'-DDT, diphenyldichloroethylene p,p'-DDE and other pesticides such as hexachlorocyclohexanes (α -HCH, β -HCH, γ -HCH), hexachlorobenzene (HCB), chlordane derivatives cis-chlordane, trans-chlordane, oxy-chlordane, cis-nonachlor and trans-nonachlor. Statistical comparisons between regions were performed only on compounds having concentrations above LOD in 70% of the samples. PCB118 congener was found to be highest in the industrial site (mean 4.97 ng/g lipids); PCB138 congener concentration was highest in the Urban 3 site (mean 4.27 ng/g lipids) and congener PCB153 was highest in the industrial and Urban 3 sites with mean concentration of 7.2 ng/g lipids and 5.89 ng/g lipids respectively. **Large differences in levels of p,p'-DDE between regions were observed with the Urban 3 and industrial sites having the highest concentrations of 645 ng/g lipids and 417 ng/g lipids, respectively;** β -HCH was found to be highest in the Rural 1 site; the γ -HCH in Rural 1 and industrial; the HCB in the Rural 1 and industrial sites and oxy-chlordane and t-NC in the Rural 2 sites. An association between levels of some contaminants and maternal age and parity was also found (Rudge et al. 2011).

Title: Monitoring of pesticide residues in human population of Nepal (2011)

ABSTRACT: Wide spread use of pesticides in the production system, persistence in the environment and their varying toxicity make them a major components of public health consideration. Pesticide residues have been reported to cause cancer, epilepsy, liver and kidney dysfunctions. Owing to the adverse effects of pesticides, international community had signed Stockholm convention which entered into force on 17th May 2004. Biological monitoring of pesticides in blood provides evidence of exposure of the body to pesticides and gives an indication of the body burden of the pesticide residues. Monitoring of organochlorines in blood is most appropriate because these pesticides are lipophilic in nature. Similarly, monitoring organophosphate concentrations in blood or blood products (serum, plasma) offers several advantages. The parent compounds could be monitored directly in blood. Nepal still has 70 MT (Metric Tones) of obsolete pesticides dumped across the country. The present study has been conducted in school children of Nepal, located adjacent to a warehouse containing 50.9 MT of obsolete pesticides since 1975, out of which 35.40 MT were organochlorines. **DDT (Dichloro Diphenyl Trichloroethane), Endosulphan and residues of chlorpyrifos were detected in blood samples with levels of 0.079, 0.098, 0.245 mg/l, respectively. Among DDT metabolites pp' DDE (Dichloro Diphenyl Dichloroethylene) and pp' DDT were detected.** Among endosulphan residues, levels of alpha- endosulphan, beta- endosulphan and endosulphan sulphate were 0.034, 0.023 and 0.041 mg/ l, respectively. Distribution of pesticides based on the basis of sex, age, food habits and rural/ urban habitation did not clearly indicate any pattern. Water, air, dust and soil might be the major sources of these pesticides in those school children of Nepal as pesticides were being continuously leaked from a warehouse and making their way into the environment. Recurrent problems like nausea, vomition etc during wind blowing were reported by the

students. **No work was previously done regarding the presence of pesticides in human blood in Nepal so far and this is the first report of its kind** (Shrestha et al. 2011).

Title: Prenatal exposure to DDT in malaria endemic region following indoor residual spraying and in non-malaria coastal regions of South Africa (2012)

ABSTRACT: Exemption was granted by the Stockholm Convention in 2004 for use of DDT by indoor residual spraying (IRS) as a malaria vector control. South Africa endorsed the use of DDT in its Malaria Control Programmes in malaria endemic regions and IRS remains a primary method of controlling malaria transmitting mosquitoes in this country. This study examines the impact of IRS on the levels of DDT and its metabolites in maternal blood of delivering women as a measure of prenatal exposure. We report on the concentrations of DDT and its metabolites (p,p'-DDE, p,p'-DDT, o,p'-DDE, o,p'-DDD, p,p'-DDD, and o,p'-DDT) in maternal plasma of 255 delivering women residing in three sites along Indian Ocean, namely in malaria endemic where IRS takes place, low risk and non-malaria sites. Concentrations of measured compounds were found to be significantly higher in the malaria endemic site ($p = 0.0001$): the geometric mean concentration (95% confidence intervals; $n = 91$) for o,p'-DDE was 9. ng/g lipids (7-10); for p,p'-DDE, 3840. ng/g lipids (3008-4902); for o,p'-DDD, 8. ng/g lipids (6-9); for p,p'-DDD, 26. ng/g lipids (20-32); for o,p'-DDT, 168. ng/g lipids (127-221) and for p,p'-DDT, 2194. ng/g lipids (1706-2823). These compounds were also detected in women residing in other sites but in lower concentrations. The maternal characteristics, age, IRS, number of children and breastfeeding were significantly associated for both p,p'-DDE and p,p'-DDT levels in the malaria area where exposure through IRS is predominant. There was no association between maternal characteristics and DDT levels in the low risk and non-malaria area. Results presented are of particular value to the policy decision makers and regulatory toxicology organizations as they characterise the extent of controlled exposure to DDT used exclusively for IRS purposes. Furthermore, findings of this study will form a base for further investigation of foetal exposure to pollutants (Channa et al. 2012).

Title: Maternal exposure to organochlorine pesticides in Western Australia (2013)

ABSTRACT: Background: Organochlorine pesticides (OCPs) persist over long periods of time. Little is known about levels of OCPs in the plasma of non smoking pregnant women in Western Australia. The aim of this study was to (1) determine exposure concentrations in a sample of pregnant women in Western Australia; (2) to determine the significant environmental, lifestyle and activity contributors to maternal exposure concentrations of OCPs and (3) to compare the measured maternal exposure concentrations with those measured in other countries. Methods: In a cross-sectional survey, 167 pregnant women located in rural and urban Western Australia provided plasma and answered questionnaires seeking information on lifestyle, demographics and the determinants of exposure to OCPs. Results: Of the 10 OCPs examined only HCB, β -HCH and p,p'DDE had concentrations above the limit of detection for more than 50% of samples. The mean level of HCB was 0.08. $\mu\text{g/L}$ (range 0.005-2.0. $\mu\text{g/L}$), β -HCH 0.18. $\mu\text{g/L}$ (range 0.04-3.16. $\mu\text{g/L}$) and p,p'DDE 1.05. $\mu\text{g/L}$, (range 0.03-17.04. $\mu\text{g/L}$). HCB concentrations were higher in women who ate seafood during pregnancy and who were older and lower among those with a history of breastfeeding. Concentrations of β -HCH were higher among women with a household income. < \$ 80,000 and lower among those with a history of breastfeeding. **Concentrations of p,p'DDE were**

higher among women who lived within 1. km of industry and lower among those with a history of breastfeeding. **Conclusions:** Concentrations of pesticides were low in Western Australian mothers compared with international studies (Reid et al. 2013).

Title: Concentrations of select persistent organic pollutants across pregnancy trimesters in maternal and in cord serum in Trujillo, Peru, (2013)

ABSTRACT: Although the production and use of some persistent organic pollutants (POPs) have been banned or highly restricted, human exposure remains a subject of investigation due to their environmental persistence. Physiological changes during pregnancy may affect the disposition of POPs in the mother's body, and thus fetal exposure. Changes in serum concentrations of organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs) across pregnancy trimesters, and trans-placental transfer to the fetus were investigated. Seventy-nine pregnant women in Trujillo, Peru were recruited in the first trimester of pregnancy, and provided blood samples for the analysis of 35 PCB congeners, 9 OCPs, and 11 polybrominated biphenyl diethers (PBDEs). Subsequently, maternal blood samples were collected in the second (n= 64) and third trimesters (n= 59), and cord blood samples (n= 50) were collected at delivery. There were statistically significant changes across trimesters ($p < 0.05$) for both fresh weight (increase) and lipid adjusted concentrations (decrease) of hexachlorobenzene (HCB), 2,2-Bis(4-chlorophenyl)-1,1-dichloroethene (p,p'-DDE), PCB-74, 118, 138-158, 153, 170, 180 and 194. Fresh weight concentrations of these POPs increased from first to third trimester by 10-28%. On the other hand lipid adjusted concentrations decreased from first to third trimester by 16-28%. Serum lipids increased from first to third trimester by 53% indicating the dilution of the POPs in the lipids. Concentrations of 2,2-Bis(4-chlorophenyl)-1,1,1-trichloroethane (p,p'-DDT), its metabolite p,p'-DDE, PCB-118, 138-158, 153, 170 and 180 above their limits of detection were measured in >60% of cord serum samples. Intra-individual correlations in maternal serum concentrations were high for most of the POPs ($\rho = 0.62-0.99$; $p < 0.05$) while correlations between maternal and cord serum concentrations were also high ($\rho = 0.68-0.99$; $p < 0.05$). **Results indicate that the disposition in the body and blood concentrations of POPs may change during pregnancy, and show trans-placental transfer of DDT, DDE and PCBs** (Adetona et al. 2013).

Title: Biomarkers of maternal and fetal exposure to organochlorine pesticides measured in pregnant hispanic women from brownsville, texas (2013)

ABSTRACT: Biomarkers of organochlorine pesticides were measured in both venous and umbilical cord blood from 35 pregnant Hispanic women living in Brownsville, Texas, USA. Gas chromatography with an electron capture detector was used to analyze specimens for 30 individual pesticides or their metabolites. Results indicate that blood concentrations were relatively low for most individual compounds, but that high-end (upper 10th percentile) values for total DDT were comparatively high. **Although health effects associated with measured blood concentrations are uncertain, there is concern that fetal exposure to low levels of these OC compounds, either individually or in combination, might contribute to subsequent health problems, including neurodevelopmental effects, cancer, endocrine disruption, obesity and diabetes** (Sexton et al. 2013).

Title: Pollutant concentrations in placenta (2013)

ABSTRACT: Unborn children are exposed to environmental pollutants via the placenta, and there is a causal relationship between maternal intake of pollutants and fetal exposure. **Placental examination is an effective way for acquiring data for estimating fetal exposure.** We analyzed the concentrations of 104 congeners of persistent organic pollutants, seven organotin compounds, five heavy metals, and methylmercury in 130 randomly selected placentas. Additionally, we examined similarities between pollutant concentrations by analyzing correlations between their placental concentrations. Our results yield new information for conducting contaminant risk assessments for the prenatal period. Out of the 117 individual persistent organic pollutants or metals assayed, 46 could be detected in more than half of the placentas. **Moreover, dichlorodiphenyldichloroethylene (p,p'-DDE) was found in all placentas. The data indicates that fetal exposure to dioxins and furans (PCDD/Fs), polychlorinated biphenyls (PCBs), p,p'-DDE, and methylmercury depends on the mother's parity, and age. We also conclude that sources of the above four pollutants are similar but differ from the sources of polybrominated diphenyl ethers (Leino et al. 2013).**

Title: Placental transfer of persistent organic pollutants: A preliminary study on mother-newborn pairs (2013)

ABSTRACT: The aim of this study was to characterize the placental transfer of some environmental pollutants, and to explore the possibility of quantitatively predicting in utero exposure to these contaminants from concentrations assessed in maternal blood. Levels of toxic substances such as pesticides (p,p'-DDE, β -HCH, and HCB), polychlorinated biphenyls (PCBs), perfluorooctane sulfonate (PFOS), and perfluorooctanoic acid (PFOA) were determined in serum samples of 38 pregnant women living in Rome and in samples of cord blood from their respective newborns. The study was carried out in the years 2008-2009. PCB mean concentrations in maternal serum and cord serum ranged from 0.058 to 0.30, and from 0.018 to 0.064 ng/g fw respectively. Arithmetic means of PFOS and PFOA concentrations in mothers and newborns were 3.2 and 1.4 ng/g fw, and 2.9 and 1.6 ng/g fw. **A strong correlation was observed between concentrations in the maternal and the foetal compartment for PFOS (Spearman $r = 0.74$, $p < 0.001$), PFOA (Spearman $r = 0.70$, $p < 0.001$), PCB 153 (Spearman $r = 0.60$, $p < 0.001$), HCB (Spearman $r = 0.68$, $p < 0.001$), PCB 180 (Spearman $r = 0.55$, $p = 0.0012$), and p,p'-DDE (Spearman $r = 0.53$, $p = 0.0099$). A weak correlation ($p < 0.1$) was observed for PCBs 118 and 138 (Porpora et al. 2013).**

Title: Assessment of the levels of persistent organic pollutants and 1-hydroxypyrene in blood and urine samples from Mexican children living in an endemic malaria area in Mexico (2012)

ABSTRACT: The aim of this study was to evaluate the exposure levels to persistent organic pollutants and 1-hydroxypyrene in children living in an endemic malaria zone in Mexico. The blood levels for 1,1,1-trichloro-2,2-bis(pchlorophenyl) ethane (DDT), 1,1-dichloro-2,2-bis(p-chlorophenyl) ethylene (DDE) and lindane ranged from 15.4 to 17,886.5 ng/g lipid, 6,624.3 to 100,119.0 ng/g lipid, and 351.1 to 6,153.8 ng/g lipid, respectively. For total polychlorinated biphenyls the blood levels ranged from 2,584.9 to 14,547.9 ng/g lipid. Regarding urinary 1-

hydroxypyrene levels, the mean level was 2.9 ± 3.1 $\mu\text{mol/mol}$ creatinine. **In conclusion, the children in our study are exposed to levels higher than normal to mixtures of environmental contaminants** (Trejo-Acevedo et al. 2012).

Title: Organochlorine pesticide residues in blood samples of agriculture and sheep wool workers in bangalore (rural), India (2012)

ABSTRACT: To describe exposure level of organochlorine pesticides (OCP) among workers occupationally engaged in agriculture and sheep wool associated jobs, the present study was carried out in rural neighborhood of Bangalore city, India. Thirty participants were interviewed and obtained informed consent before blood sample collection. **The maximum concentrations of OCP were detected in blood samples of agriculture workers than sheep wool workers. Among the metabolites of HCH and DDT, lindane (c-HCH) and p,p'-DDE were the most contributed to the total OCP. There were no differences in pesticide residues found between sex and work groups. It was observed that about 30% of samples exceeded the tolerance limits of 10 $\mu\text{g/L}$ prescribed for HCH under the prevention of food adulteration act. Therefore, the present study recommends continuous monitoring with larger sample size** (Dhananjayan, Ravichandran and Rajmohan 2012)

Title: Organochlorine pesticide residue levels in blood serum of inhabitants from Veracruz, Mexico (2012)

ABSTRACT: The objective of the present study was to monitor the levels of organochlorine pesticides HCB; α -, β -, γ -HCH; pp'DDE; op'DDT; and pp' DDT in blood serum of Veracruz, Mexico inhabitants. Organochlorine pesticides were analyzed in 150 blood serum samples that constituted that which remained after clinical analyses, using gas chromatography-electron-capture detection (GC-ECD). The results were expressed as milligrams per kilogram on fat basis and micrograms per liter on wet weight. Only the following pesticides were detected: p,p'-DDE was the major organochlorine component, detected in 100% of samples at mean 15.8 mg/kg and 8.4 $\mu\text{g/L}$; p,p'-DDT was presented in 41.3.% of monitored samples at mean 3.1 mg/kg and 1.4 $\mu\text{g/L}$; β -HCH was found in 48.6% of the samples at mean 4.9 mg/kg and 2.7 $\mu\text{g/L}$; op'DDT was determined to be in only 3.3% of monitored samples at mean 2.7 mg/kg and 1.4 $\mu\text{g/L}$. The pooled samples divided according to sex showed significant differences of β -HCH and pp'DDE concentrations in females. The samples grouped according to age presented the third tertile as more contaminated in both sexes, indicating age as a positively associated factor with serum organochlorine pesticide levels in Veracruz inhabitants (Waliszewski 2012) (01).

Title: Serum concentrations of p,p'-dichlorodiphenyltrichloroethane (p,p'-DDE) in a sample of agricultural workers from Bolivia (2013)

ABSTRACT: Organochlorine pesticide p,p'-dichlorodiphenyltrichloroethane (DDT) is still used for vector control in several tropical and subtropical areas of South America and there is

evidence of recent illegal use in agriculture. Its main breakdown product in the environment and living organisms is p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE), which is considered a marker of past exposure to DDT. The aim of the present study was to assess human exposure to p,p'-DDE in a sample of agricultural farmers from three rural communities in eastern Bolivia. In addition, o,p'-DDT was analyzed as a surrogate of a potential ongoing exposure to the pesticide. Face-to-face questionnaires were performed, and serum samples were analyzed by high-resolution gas chromatography with mass spectrometry. p,p'-DDE was found in 100% of the samples, with a median concentration of 19.7ngmL⁻¹ (4788.7ng/g lipid), while o,p'-DDT was detected in 3 samples (4.3%). Serum p,p'-DDE concentrations were associated with time of residence in the study area, personal hygiene after work, and body mass index in adjusted multinomial logistic regression models with tertiles of p,p'-DDE as the dependent variable. **The present results revealed high levels of exposure to p,p'-DDE, which might be derived from a heavily polluted local environment and past occupational exposure. These findings deserve further attention due to the potential associated health risks and point to the need for the continuous monitoring of these populations** (Mercado et al. 2013).

Title: Concentrations of organochlorine pesticides (OCPs) in human blood plasma from Hong Kong: Markers of exposure and sources from fish (2013)

ABSTRACT: Previous studies revealed that food, particularly fish products, is the major source for human exposure to organochlorine pesticides (OCPs). Our previous studies revealed that contamination of Hong Kong market fish with DDT was 0.74-131 with a mean of 12.2ngg⁻¹, ww, a result suggested that local people might be exposed to hazardous concentrations of OCPs. Therefore, the present systematic study was conducted to determine concentrations of OCPs in blood plasma of Hong Kong residents, develop marker substances and evaluate sources of 19 individual OCPs from fish. Concentrations of Σ OCPs, Σ DDTs and Σ HCHs ranged from 294 to 9732, 172 to 8842, and 115 to 1616ngg⁻¹ lipid weight (lw), respectively. These concentrations were greater than those in blood of people from most developed countries but lower than those from most developing countries. The upper age group (>50years) had significant ($p < 0.05$) greater concentrations of OCPs than other groups. Furthermore, concentrations of OCPs in males were significantly ($p < 0.05$) greater than those in females. p, p'-DDE was the predominant congener and marker substance of DDTs, while β -HCH was the predominant congener and marker substance of HCHs. p, p'-DDE was more correlated with Σ OCPs ($r^2=0.830$, $p < 0.05$) than other individual OCPs, which suggested that p, p'-DDE is a good marker for accumulation of OCPs in blood plasma. **Concentrations of individual OCPs were significantly correlated with not only their corresponding total concentrations in fishes from Hong Kong markets ($r^2=0.391$, $p=0.024$), but also their bioaccessible fractions, which were estimated by an in vitro digestion method ($r^2=0.784$, $p=0.000$).** These results suggested that the in vitro gastrointestinal model is a more accurate method to evaluate accumulation of and health risks caused by dietary intake of OCPs. This study, which was the first systematic study to investigate concentrations of OCPs in blood of Hong Kong people, provides a baseline to which future measurements can be compared (Wang et al. 2013a).

12.7.1.1 Blood plasma levels and blood pressure

Title: Associations between plasma persistent organic pollutant levels and blood pressure in Inuit adults from Nunavik (2013)

ABSTRACT: Background: Recent evidence suggests that exposure to persistent organic pollutants (POPs) increases the risk of hypertension in environmentally exposed populations. High POP levels have been detected in Arctic populations and the exposure is related to high consumption of fish and marine mammals, which represent the traditional diet of these populations. Objective: We examined the associations between polychlorinated biphenyls (PCBs), organochlorine (OC) pesticides and hypertension among Inuit from Nunavik (Quebec, Canada). Methods: A complete set of data was obtained for 315 Inuit ≥ 18 years who participated in the "Santé Québec" health survey that was conducted in the 14 villages of Nunavik in 1992. Fourteen polychlorinated biphenyls (PCBs) and 8 OC pesticides or their metabolites were measured in plasma samples using gas chromatography with electron capture detection. Blood pressure (BP) was measured using a standardized protocol and information regarding anti-hypertensive medication was obtained through questionnaires. The associations between log-transformed POPs and hypertension (systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg or anti-hypertensive medication) were analyzed using multiple logistic regressions. Results: Total PCBs as well as the sum of non-dioxin-like PCBs were significantly associated with higher risk of hypertension. Furthermore, the risk of hypertension increased with higher plasma concentrations of congeners 101, 105, 138 and 187. Models adjusted for BP risk factors became significant after including n-3 polyunsaturated fatty acids (PUFAs) and further adjustment for lead and mercury did not change the results. **Regarding OC pesticides, p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE) was associated with increased risk of hypertension while inverse associations were observed with p,p'-dichlorodiphenyltrichloroethane (p,p'-DDT), β -hexachlorocyclohexane (HCH) and oxychlordan.** Conclusions: Some PCB congeners were associated with higher risk of hypertension in this highly exposed population. Most associations became significant after including n-3 PUFAs in the models. However, the analyses of OC pesticides revealed divergent results, which need to be confirmed in further cohort and experimental studies (Valera et al. 2013a).

Title: Exposure to persistent organic pollutants and risk of hypertension among Inuit from Greenland(2013)

ABSTRACT: Background: Exposure to persistent organic pollutants (POPs) is of concern in Arctic populations since these contaminants accumulate in fish and marine mammals, which is an important part of the traditional diet of these populations. Epidemiological and experimental studies have reported significant associations between POPs and increased blood pressure (BP) in populations with different degrees of exposure. Objective: We aimed to assess the risk of hypertension related to increasing levels of polychlorinated biphenyls (PCBs) and organochlorine (OC) pesticides. Methods: Fifteen PCBs and 11 OC pesticides or their metabolites were determined in plasma of 1614 Inuit adults ≥ 18 years living in 9 towns and 13 villages in Greenland. BP was measured using a standardized protocol. The risk of hypertension was estimated through logistic regression using POPs as continuous variables (log-transformed). Hypertension was defined as systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg and/or antihypertensive treatment. Results: Overall, the odd ratios (ORs) of hypertension were not statistically significant for dioxin-like PCBs, non-dioxin-like PCBs and OC pesticides after adjusting for confounders. Once the analyses were stratified by age category (18-39 and ≥ 40 years), increased risk of hypertension was observed for total dioxin-

like PCBs among the youngest [OR: 1.34 (95% CI: 1.03-1.74)] while a borderline protective effect was observed for total non-dioxin-like PCBs [OR: 0.81 (95% CI: 0.66-0.99)] among the oldest. **Higher risk of hypertension was also associated with increasing p, p'-dichlorodiphenyltrichloroethane (DDT) concentrations among the youngest [OR: 1.42 (95% CI: 1.08-1.85)]. Conclusion: Overall, no significant associations were observed between PCBs, OC pesticides and blood pressure in this highly exposed population although the associations differed by age category (Valera et al. 2013b).**

12.7.2 Adipose tissue

Title: Monitoring of organochlorine pesticide residue levels in adipose tissue of Veracruz, Mexico inhabitants (2011)

ABSTRACT: The objective of the present study was to monitor the levels of organochlorine pesticides HCB, α - β - γ -HCH, pp'DDE, op'DDT and pp'DDT in 150 adipose tissue samples of Veracruz, Mexico inhabitants. In analyzed samples, the following pesticides were detected: p,p'-DDE in 100% of the samples at mean 1.643 mg/kg; p,p'-DDT in 99.3.% of the samples at mean 0.227 mg/kg; β -HCH in 97.3% of the samples at mean 0.063 mg/kg; and op'DDT in 93.3% of the samples at mean 0.022 mg/kg. Comparing mean, median and geometric mean concentrations of organochlorine pesticides shows a decrease in values from mean to median and to geometric mean which points out a prevalence of lower concentrations among the total samples and the existence of occasional cases of extreme exposure expressed in range values. The pooled samples divided according to sex, showed only significant differences of pp'DDE median concentrations between sexes. The other organochlorine pesticides indicated no statistical differences between sexes, including the pp'DDE/pp'DDT ratio. The samples grouped according to age, showed that the third tertile was more contaminated for both sexes, indicating age as a positively associated factor with organochlorine pesticide levels in adipose tissue of Veracruz inhabitants. **Comparing organochlorine pesticide levels between 2008 and 2010 years, a decreased tendency for β -HCH, pp'DDE, Σ -DDT and pp'DDE/pp'DDT ratio levels was observed (Waliszewski et al. 2011).**

Title: Levels of Organochlorine Pesticides Residues in Human Adipose Tissue, Data from Tabasco, Mexico

ABSTRACT: The objective of this study was to determine the levels of organochlorine pesticides HCB, α - β - γ -HCH, p,p'-DDE, o,p'-DDT and p,p'-DDT in 150 adipose tissue of inhabitants of Tabasco, Mexico. The following pesticides were detected: p,p'-DDE in 100 % of samples at mean 1.034 mg/kg; p,p'-DDT in 96.7 % at mean 0.116 mg/kg; o,p'-DDT in 78.7 % at mean 0.022 mg/kg and β -HCH in 58.0 % at mean 0.049 mg/kg. The pooled sample was divided according to sex of donors (75 female and 75 male). Significantly higher levels of all organochlorine pesticides in females were found. **The sample was divided into three age's ranges (15-28, 29-45 and 46-84 years). The mean and median levels of β -HCH, p,p'-DDE and Σ -DDT increase significantly ($p < 0.05$) from the first to the second and third group. The presence of organochlorine pesticide residues in Tabasco inhabitants is still observed, indicating sources of exposure to the pesticides (Waliszewski et al. 2012) (02).**

Title: Organochlorine pesticide levels in female adipose tissue from Puebla, Mexico (2012)

ABSTRACT: The objective of this study was to determine the levels of organochlorine pesticides HCB, α - β - γ -HCH, pp'DDE, op'DDT and pp'DDT in adipose tissue of females living in Puebla, Mexico. Organochlorine pesticides were analyzed in 75 abdominal adipose tissue samples taken during 2010 by autopsy at the Forensic Services of Puebla. The results were expressed as mg/kg on fat basis. In analyzed samples the following pesticides were detected: p,p'-DDE in 100% of samples at mean 1.464 mg/kg; p,p'-DDT in 96.0.% of samples at mean 0.105 mg/kg; op'DDT in 89.3% of monitored samples at mean 0.025 mg/kg and β -HCH in 94.7% of the samples at mean 0.108 mg/kg. To show if organochlorine pesticide levels in monitored female's adipose tissues are age dependant, the group was divided in three ages ranges (13-26, 26-57 and 57-96 years). The mean and median levels of all organochlorine pesticides increase significantly ($p < 0.05$) from the first to second and from the first to third group. At the same time, the increase of mean and medians levels from the second to third group were not statistically significant ($p > 0.05$). The present results compared to previous ones from 2008 indicates an increase in the concentrations during the 2010 study, but only the differences for pp'DDE and op'DDT were statistically significant. The 2010 group of females was older compared to the 2008 group. **The presence of organochlorine pesticide residues is still observed, indicating uniform and permanent exposure to the pesticides by Puebla inhabitants** (Waliszewski et al. 2012) (03).

Title: Accumulation levels and characteristics of some pesticides in human adipose tissue samples from Southeast China (2011)

ABSTRACT: This paper presents a comprehensive study of pesticide levels and bio-accumulation characteristics in human adipose tissues among residents of Southeast China. A large number of adipose samples ($n=633$) were selected for 58 pesticides and were analyzed by high sensitive Gas Chromatography-Tandem Mass Spectrometry (GC-MS/MS). The results showed that POPs pesticides were frequently detected, including 2,4'-DDD, 2,4'-DDE, 2,4'-DDT, 4,4'-DDD, 4,4'-DDE, 4,4'-DDT, α -HCH, β -HCH, γ -HCH, δ -HCH, hexachlorobenzene (HCB), and mirex. Other detected pesticide species were dicofol, methamidophos and chlordimeform, which have rarely been reported. Comparing to different countries, the concentrations of total DDT and HCH in these three Chinese southeastern sites were in the middle range, whereas the HCB and mirex were in the lower end. A significant correlation was observed between region as well as age and POPs pesticide levels. Some pesticide residue levels were also found significantly correlated to occupation. However, there was no significant correlation between gender and pesticides. **Meanwhile, it is interesting to find that mortality of malignant tumors tends to associate with the pesticides levels in human adipose tissue. More importantly, the measured data presented in this study provide realistic information which is useful for assessing human exposure to pesticides in the general population of Southeast China** (Wang et al. 2011)

Title: Determination of organochlorine pesticides residues in human adipose tissue, data from Cukurova, Turkey (2010)

ABSTRACT: We determined and compared the levels of BHC and DDT isomers and metabolites and HCB in the adipose tissue of 82 cases of autopsies performed at the Morgue Department of Adana Branch of the Council of Forensic Medicine. The relationships between the age, gender, and body mass indexes of cases, and the accumulation of OCs residues were also investigated. Detectable concentrations of p,p'-DDE were found in 100% of adipose tissue samples. Concentrations of OCs in female adipose tissues were significantly higher than male adipose tissues ($p < 0.05$). **The presented work is highly significant, being the first study pointing out the chronic exposure to organochlorine pesticides in Cukurova (Turkey) region** (Daglioglu et al. 2010).

Title: Organochlorine pesticide levels in adipose tissue of pregnant women in Veracruz, Mexico (2010)

ABSTRACT: DDT and Lindane (γ -HCH) which were used until 1999 in Mexico, have provided great benefits in the combat of vectors that spread infection-borne diseases and in agriculture for crop protection. The persistence in the environment and their accumulative properties results in bioconcentration in lipid rich tissues of the human body that reflect the extent of environmental pollution. Human adipose tissue samples were taken during 2009 from abdominal cavities of 69 pregnant women by cesarean surgery and from 34 samples of control donors by autopsy in Veracruz State. The samples were analyzed by gas chromatography with ECD. The results of mean levels (mg/kg on fat basis) were higher in controls compared to pregnant women β -HCH 0.064 vs 0.027; pp'DDE 1.187 vs. 0.745; op'DDT 0.016 vs. 0.011; pp'DDT 0.117 vs. 0.099 and Σ -DDT 1.337 vs. 0.854. **The pregnant women group was divided according to age: up to 20, 20-30, and more than 30 years, and presented an increase for the more persistent pesticides with age in terms of mean concentrations and a more pronounced higher correlation in medians levels. Pairing Body Mass Index to organochlorine pesticide mean levels revealed no correlation between these factors in pregnant women** (Herrero-Mercado et al. 2010).

Title: Predictors of adipose tissue concentrations of organochlorine pesticides in a general Danish population (2012)

ABSTRACT: Organochlorine pesticides are ubiquitously present in the environment and suspected of carcinogenic, neurological and immunological effects. Our objective was to identify determinants of adipose tissue levels of organochlorine pesticides experienced by a general Danish population. Adipose tissue was collected upon enrolment of 245 randomly selected persons from a prospective cohort of 57,053 persons enrolled between 1993 and 1997. We examined geography, gender, age, lactation, body mass index (BMI) and intake of nine dietary groups and tap water drinks, as potential determinants of dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene, hexachlorocyclohexane, dieldrin, hexachlorobenzene, cis-nonachlor, trans-nonachlor and oxychlordane. Living in Copenhagen city and age at enrolment showed positive associations

with all compounds. BMI was positively associated with all compounds except cis-nonachlor. Fatty-fish consumption showed positive associations with cis-nonachlor, trans-nonachlor, DDT and dieldrin and fruit and vegetables were inversely associated with dieldrin. Determinant estimates of trans-nonachlor were similar to estimates of total chlordanes while cis-nonachlor and oxychlordane seemed to differ. **This is one of the first studies of organochlorine pesticides predictors in adipose tissue and contributes to the ongoing debate about exposure sources of these compounds. Single determinants varied among the individual compounds, even within related chlordanes residues, suggesting that organochlorine pesticides should not be treated as a homogenous group** (Bräuner et al. 2012) (02).

Title: Increased proliferative effect of organochlorine compounds on human preadipocytes (2012)

ABSTRACT: Chlorinated persistent organic pollutants, commonly referred to as organochlorine compounds (OCs), are chemicals of environmental concern that were mostly used historically as pesticides, solvents, flame retardants, and other applications, though some still continue to be produced. OCs accumulate in adipose tissue because of their hydrophobicity. Evidence suggests that OCs modulate adipose tissue metabolism and could affect its development. At the cellular level, the development of adipose tissue is partly controlled by replication of preadipocytes, which may in turn be modulated by contaminants. The aim of this study was to determine whether exposure to specific OCs and to different concentrations, some mimicking those achieved in human tissues that are exposed to chemicals from the environment, affects human preadipocyte proliferation capacity. Human preadipocytes were exposed to various concentrations (3-500 µM) of highly prevalent OCs (PCBs 77, 153 and DDE) for 48 h. At the end of the exposure period, quantification of cell density was assessed by a cell proliferation ELISA assay. Preadipocyte proliferation significantly increased (~28-72%) in response to most of the concentrations of PCB 153 and DDE as compared to the control. **These findings suggest that exposure to some OCs and concentrations increase the proliferative capacity of human preadipocytes** (Chapados et al. 2012).

12.7.1 Known residents of sprayed houses 229

12.7.2 General population living in areas using indoor residual spraying 233

Title: Assessment of nonoccupational exposure to DDT in the tropics and the north: Relevance of uptake via inhalation from indoor residual spraying (2011=

ABSTRACT: Background: People who live in dwellings treated with indoor residual spraying (IRS) of DDT [1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane] for disease-vector control in the tropics and indigenous populations in the Arctic who consume marine mammals experience high nonoccupational exposure to DDT. Although the use of DDT in IRS is rising, the

resulting nonoccupational exposure is poorly characterized. Objectives: We have provided a comparative assessment of exposure to DDT and its metabolites in the general population of the tropical and northern regions and in highly exposed populations in these regions. Methods: We compiled > 600 average or median DDT concentrations from the peer-reviewed literature, representing > 23,000 individual measurements in humans, food, air, soil, and dust. We use Monte Carlo sampling of distributions based on these data to estimate distributions of population- and route-specific uptake. We evaluate our exposure estimates by comparing them with biomonitoring data. Results: DDT concentrations are highest in people living in IRS-treated houses and lowest in the northern general population, differing by a factor of about 60. Inuits and the general population in the tropics have similar concentrations. Inhalation exposure explains most of the difference in concentration between the highly exposed and the general population in the Tropics. Calculated exposure levels are consistent with human biomonitoring data. Conclusions: **Nonoccupational inhalation exposure is a relevant exposure pathway for people living in homes treated by IRS of DDT. Continued monitoring of time trends and DDE to DDT ratios in the Tropics and in the North is needed to identify a possible slowdown in concentration decline and the influence of ongoing DDT use** (Ritter et al. 2011).

12.7.2.1 Health risk assessment of applicators to DDT during indoor residual spraying

Title: *Exposure and health risk assessment of applicators to DDT during indoor residual spraying in malaria vector control program (2012)*

ABSTRACT: We assessed exposure of applicators, health risk of DDT to the applicators and evaluated the applicability of existing pesticide exposure models for indoor residual spraying (IRS). Patch sampling for dermal and personal air sampler for inhalation exposure were used in monitoring 57 applicators on the exposure assessment to DDT. The exposure of the applicators was also estimated using three exposure models. The mean actual dermal exposure was 449 mg total DDT per applicator per one house treatment. The applicators were exposed to DDT much beyond the estimated AOEL (acceptable operator exposure level) of DDT. The exposure estimated with ConsExpo 5.0 b01 model is situated between the median and the 75th percentile of the experimental data. On the other hand, spraying model 1 and spraying model 10 overestimate the exposure. Thus, these three models cannot be directly used for the particular circumstances of IRS as a tool for risk assessment. **In general, use of DDT in IRS as a control method for malaria mosquitoes holds a high health risk for the applicators. Strict implementation of spraying procedures stated in the IRS manual of World Health Organization (WHO) is necessary to reduce the exposure level and health risk of applicators to DDT** (Wassie et al. 2012).

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REFERENCES

- Adetona, O.A , Horton, K.A , Sjodin, A.C , Jones, R.C , Hall, D.B.D , Aguillar-Villalobos, M.E , Cassidy, B.E.A , Vena, J.E.F , Needham, L.L.C , Naeher, L.P.A (2013)
Concentrations of select persistent organic pollutants across pregnancy trimesters in maternal and in cord serum in Trujillo, Peru
Chemosphere, 91 (10), pp. 1426-1433.
- Aguilar-Garduño, C., Lacasaña, M., Blanco-Muñoz, J., Rodríguez-Barranco, M., Hernández, A.F., Bassol, S., González-Alzaga, B., Cebrián, M.E. (2013)
Changes in male hormone profile after occupational organophosphate exposure. A longitudinal study.
Toxicology, 307, pp. 55-65.
- Al-Saleh, I., Al-Doush, I., Alsabbaheen, A., Mohamed, G.E.D., Rabbah, A. (2012)
Levels of DDT and its metabolites in placenta, maternal and cord blood and their potential influence on neonatal anthropometric measures
Science of the Total Environment, 416, pp. 62-74.
- Ankley, G.T., Gray, L.E. (2013)
Cross-species conservation of endocrine pathways: A critical analysis of tier 1 fish and rat screening assays with 12 model chemicals.
Environmental Toxicology and Chemistry, 32 (5), pp. 1084-1087.
- Aronson, K.J., Wilson, J.W.L., Hamel, M., Diarsvitri, W., Fan, W., Woolcott, C., Heaton, J.P.W., Nickel, J.C., MacNeily, A., Morales, A. (2010)
Plasma organochlorine levels and prostate cancer risk.
Journal of Exposure Science and Environmental Epidemiology, 20 (5), pp. 434-445.
- Arrebola, J.P., Pumarega, J., Gasull, M., Fernandez, M.F., Martin-Olmedo, P., Molina-Molina, J.M., Fernández-Rodríguez, M., Porta, M., Olea, N. (2013)
Adipose tissue concentrations of persistent organic pollutants and prevalence of type 2 diabetes in adults from Southern Spain.
Environmental Research, 122, pp. 31-37.
- Avivar Oyonarte, C., Durán Salas, I., Molina Arrebola, M.A., Castilla Alcalá, J.A., Olea Serrano, N., Fernández Cabrera, M. (2010)
Pesticide exposure and decreased sperm count [La exposición a plaguicidas se asocia con la disminución del recuento espermático].
Revista del Laboratorio Clínico, 3 (1), pp. 4-11.
- Bachelet, D., Verner, M.-A., Guihenneuc-Jouyau, C., Charlier, C., Charbonneau, M., Haddad, S., Guénel, P. (2010)
Assessment of exposure to persistent organochlorine compounds in epidemiological studies on breast cancer: A literature review and perspectives for the Cecile study.
Acta Clinica Belgica, 65 (SUPPL. 1), pp. 49-57.

Baker, S., Vinayaka, A.C., Manonmani, H.K., Thakur, M.S. (2012)
Development of dipstick-based immuno-chemiluminescence techniques for the
rapid detection of dichlorodiphenyltrichloroethane.
Luminescence, Article in Press.

Band, P.R., Abanto, Z., Bert, J., Lang, B., Fang, R., Gallagher, R.P., Le,
N.D. (2011)
Prostate cancer risk and exposure to pesticides in British Columbia
Farmers.
Prostate, 71 (2), pp. 168-183.

Bedi, J.S.A., Gill, J.P.S.A., Aulakh, R.S.A., Kaur, P.A., Sharma, A.A.,
Pooni, P.A.B. (2013)
Pesticide residues in human breast milk: Risk assessment for infants from
Punjab, India.
Science of the Total Environment, 463-464, pp. 720-726.

Bergkvist, C.A., Aune, M.B, Nilsson, I.B, Sandanger, T.M.C.D., Hamadani,
J.D.E, Tofail, F.E, Oyvind-Odland, J.C, Kabir, I.E, Vahter, M.A (2012)
Occurrence and levels of organochlorine compounds in human breast milk in
Bangladesh.
Chemosphere, 88 (7), pp. 784-790.

Bergonzi, R., De Palma, G., Specchia, C., Dinolfo, M., Tomasi, C., Frusca,
T., Apostoli, P. (2011)
Persistent organochlorine compounds in fetal and maternal tissues:
Evaluation of their potential influence on several indicators of fetal
growth and health.
Science of the Total Environment, 409 (15), pp. 2888-2893.

Bimenya, G.S., Harabulema, M., Okot, J.P., Francis, O., Lugemwa, M., Okwi,
A.L. (2010)
Plasma levels of DDE/DDT and liver function in malaria control personnel 6
months after indoor residual spraying with DDT in northern Uganda.
South African Medical Journal, 100 (2), pp. 118-121.

Blanco-Muñoz, J., Lacasaña, M., Aguilar-Garduño, C., Rodríguez-Barranco,
M., Bassol, S., Cebrián, M.E., López-Flores, I., Ruiz-Pérez, I. (2011)
Effect of exposure to p,p'-DDE on male hormone profile in Mexican flower
growers.
Occupational and Environmental Medicine, Article in Press.

Boada, L. D., Zumbado M. et al. (2012).
Complex organochlorine pesticide mixtures as determinant factor for breast
cancer risk: A population-based case-control study in the Canary Islands
(Spain).
Environmental Health: A Global Access Science Source 11(1).

Bouwman, H., Kylin, H., Sereda, B., Bornman, R. (2012)
High levels of DDT in breast milk: Intake, risk, lactation duration, and
involvement of gender.
Environmental Pollution, 170, pp. 63-70.

Bräuner, E.V., Sørensen, M., Gaudreau, E., Leblanc, A., Eriksen, K.T., Tjønneland, A., Overvad, K., Raaschou-Nielsen, O. (2012) (01)
A prospective study of organochlorines in adipose tissue and risk of non-Hodgkin lymphoma.
Environmental Health Perspectives, 120 (1), pp. 105-111.

Bräuner, E.V., Raaschou-Nielsen, O., Gaudreau, E., Leblanc, A., Tjønneland, A., Overvad, K., Sørensen, M. (2012) (02)
Predictors of adipose tissue concentrations of organochlorine pesticides in a general Danish population.
Journal of Exposure Science and Environmental Epidemiology, 22 (1), pp. 52-59.

Burns, J.S., Williams, P.L., Sergeev, O.S., Korrick, S.A., Lee, M.M., Revich, B., Altshul, L., del Prato, J.T., Humble, O., Patterson Jr., D.G., Turner, W.E., Starovoytov, M., Hauser, R. (2012)
Serum concentrations of organochlorine pesticides and growth among Russian boys.
Environmental Health Perspectives, 120 (2), pp. 303-308.

Burns, C.J., McIntosh, L.J., Mink, P.J., Jurek, A.M., Li, A.A. (2013)
Pesticide exposure and neurodevelopmental outcomes: Review of the epidemiologic and animal studies.
Journal of Toxicology and Environmental Health - Part B: Critical Reviews, 16 (3-4), pp. 127-183.

Canales-Aguirre, A., Padilla-Camberos, E., Gómez-Pinedo, U., Salado-Ponce, H., Feria-Velasco, A., de Celis, R. (2011)
Genotoxic effect of chronic exposure to DDT on lymphocytes, oral mucosa and breast cells of female rats.
International Journal of Environmental Research and Public Health, 8 (2), pp. 540-553.

Cárdenas-González, M.a , Gaspar-Ramírez, O.a , Pérez-Vázquez, F.J.a , Alegría-Torres, J.A.a , González-Amaro, R.b , Pérez-Maldonado, I.N.a (2012)
p,p'-DDE, a DDT metabolite, induces proinflammatory molecules in human peripheral blood mononuclear cells "in vitro".
Experimental and Toxicologic Pathology, . Article in Press.

Castellanos, C.G., Sørvik, I.B., Tanum, M.B., Verhaegen, S., Brandt, I., Ropstad, E. (2013)
Differential effects of the persistent DDT metabolite methylsulfonyl-DDE in nonstimulated and LH-stimulated neonatal porcine Leydig cells.
Toxicology and Applied Pharmacology, 267 (3), pp. 247-255.

Channa, K., Röllin, H.B., Nøst, T.H., Odland, J.Ø., Sandanger, T.M. (2012)
Prenatal exposure to DDT in malaria endemic region following indoor residual spraying and in non-malaria coastal regions of South Africa.
Science of the Total Environment, 429, pp. 183-190.

Chapados, N.A., Casimiro, C., Robidoux, M.A., Haman, F., Batal, M., Blais, J.M., Imbeault, P. (2012)
Increased proliferative effect of organochlorine compounds on human preadipocytes.
Molecular and Cellular Biochemistry, 365 (1-2), pp. 275-278.

Chaturvedi, N.K., Kumar, S., Negi, S., Tyagi, R.K. (2010) Endocrine disruptors provoke differential modulatory responses on androgen receptor and pregnane and xenobiotic receptor: Potential implications in metabolic disorders.
Molecular and Cellular Biochemistry, 345 (1-2), pp. 291-308.

Chevrier, C., Warembourg, C., Gaudreau, E., Monfort, C., Le Blanc, A., Guldner, L., Cordier, S. (2013)
Organochlorine pesticides, polychlorinated biphenyls, seafood consumption, and time-to-pregnancy.
Epidemiology, 24 (2), pp. 251-260.

Cook, M.B., Trabert, B., McGlynn, K.A. (2011)
Organochlorine compounds and testicular dysgenesis syndrome: Human data.
International Journal of Andrology, 34 (4 PART 2), pp. e68-e85.

Çok, I., Yelken, Ç., Durmaz, E., Üner, M., Sever, B., Satır, F. (2011)
Polychlorinated biphenyl and organochlorine pesticide levels in human breast Milk from the mediterranean city Antalya, Turkey.
Bulletin of Environmental Contamination and Toxicology, 86 (4), pp. 423-427.

Cupul-Uicab, L.A., Hernández-Ávila, M., Terrazas-Medina, E.A., Pennell, M.L., Longnecker, M.P. (2010)
Prenatal exposure to the major DDT metabolite 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) and growth in boys from Mexico.
Environmental Research, 110 (6), pp. 595-603.

Cupul-Uicab, L.A., Klebanoff, M.A., Brock, J.W., Longnecker, M.P. (2013)
Prenatal exposure to persistent organochlorines and childhood obesity in the U.S. collaborative perinatal project.
Environmental Health Perspectives, 121 (9), pp. 1103-1109.

Daglioglu, N., Gulmen, M.K., Akcan, R., Efeoglu, P., Yener, F., Unal, I. (2010)
Determination of organochlorine pesticides residues in human adipose tissue, data from cukurova, turkey.
Bulletin of Environmental Contamination and Toxicology, 85 (1), pp. 97-102.

Dar, S.A., Das, S., Ramachandran, V.G., Bhattacharya, S.N., Mustafa, M.D., Banerjee, B.D., Verma, P. (2012)
Alterations in T-lymphocyte sub-set profiles and cytokine secretion by PBMC of systemic lupus erythematosus patients upon in vitro exposure to organochlorine pesticides.
Journal of Immunotoxicology, 9 (1), pp. 85-95.

Den Hond, E., Dhooge, W., Bruckers, L., Schoeters, G., Nelen, V., Van De Mieroop, E., Koppen, G., Bilau, M., Schroijsen, C., Keune, H., Baeyens, W., Van Larebeke, N. (2011)
Internal exposure to pollutants and sexual maturation in Flemish adolescents.
Journal of Exposure Science and Environmental Epidemiology, 21 (3), pp. 224-233.

- Dewan, P., Jain, V., Gupta, P., Banerjee, B.D. (2013)
Organochlorine pesticide residues in maternal blood, cord blood, placenta, and breastmilk and their relation to birth size.
Chemosphere, 90 (5), pp. 1704-1710.
- Dhananjayan, V., Ravichandran, B., Rajmohan, H.R. (2012)
Organochlorine pesticide residues in blood samples of agriculture and sheep wool workers in bangalore (rural), India.
Bulletin of Environmental Contamination and Toxicology, 88 (4), pp. 497-500.
- DiPietro, J.A., Davis, M.F., Costigan, K.A., Barr, D.B. (2013)
Fetal heart rate and motor activity associations with maternal organochlorine levels: results of an exploratory study.
Journal of Exposure Science and Environmental Epidemiology. Article in Press.
- Domínguez-Cortinas, G., Díaz-Barriga, F., Martínez-Salinas, R.I., Cossío, P., Pérez-Maldonado, I.N. (2012)
Exposure to chemical mixtures in Mexican children: high-risk scenarios.
Environmental Science and Pollution Research, pp. 1-7. Article in Press.
- Dominguez-Lopez, P., L. Diaz-Cueto, et al. (2012).
Differential Effect of DDT, DDE, and DDD on COX-2 Expression in the Human Trophoblast Derived HTR-8/SVneo Cells.
Journal of Biochemical and Molecular Toxicology 26(11): 454-460.
- Emeville, E., Giton, F., Giusti, A., Oliva, A., Fiet, J., Thomé, J.-P., Blanchet, P., Multigner, L. (2013)
Persistent Organochlorine Pollutants with Endocrine Activity and Blood Steroid Hormone Levels in Middle-Aged Men.
PLoS ONE, 8 (6), art. no. e66460.
- Ertl, H., Butte, W. (2012)
Bioaccessibility of pesticides and polychlorinated biphenyls from house dust: in-vitro methods and human exposure assessment.
Journal of Exposure Science and Environmental Epidemiology, . Article in Press.
- Eskenazi, B., Weldon, R.H., Webster, M., Harley, K.G., Bradman, A., Fenster, L., Davis, M.D., Hubbard, A., Barr, D.B., Holland, N. (2010)
Serum persistent organic pollutants and duration of lactation among Mexican-American women.
Journal of Environmental and Public Health, 2010, art. no. 861757.
- Garced, S., Torres-Sánchez, L., Cebrián, M.E., Claudio, L., López-Carrillo, L. (2012)
Prenatal dichlorodiphenyldichloroethylene (DDE) exposure and child growth during the first year of life.
Environmental Research, 113, pp. 58-62.

Gascon, M., Vrijheid, M., Martínez, D., Ballester, F., Basterrechea, M., Blarduni, E., Esplugues, A., Vizcaino, E., Grimalt, J.O., Morales, E., Sunyer, J. (2012)

Pre-natal exposure to dichlorodiphenyldichloroethylene and infant lower respiratory tract infections and wheeze.

European Respiratory Journal, 39 (5), pp. 1188-1196.

Gascon, M., Morales, E., Sunyer, J., Vrijheid, M. (2013a)

Effects of persistent organic pollutants on the developing respiratory and immune systems: A systematic review.

Environment International, 52, pp. 51-65.

Gascon, M., Verner, M.-A., Guzens, M., Grimalt, J.O., Forns, J., Ibarluzea, J., Lertxundi, N., Ballester, F., Llop, S., Haddad, S., Sunyer, J., Vrijheid, M. (2013b)

Evaluating the neurotoxic effects of lactational exposure to persistent organic pollutants (POPs) in Spanish children.

NeuroToxicology, 34 (1), pp. 9-15.

Gaspari, L., Sampaio, D.R., Paris, F., Audran, F., Orsini, M., Neto, J.B., Sultan, C. (2012)

High prevalence of micropenis in 2710 male newborns from an intensive-use pesticide area of Northeastern Brazil.

International Journal of Andrology, 35 (3), pp. 253-264.

Gasull, M., Pumarega, J., Téllez-Plaza, M., Castell, C., Tresserras, R., Lee, D.H., Porta, M. (2012)

Blood concentrations of persistent organic pollutants and prediabetes and diabetes in the general population of Catalonia.

Environmental Science and Technology, 46 (14), pp. 7799-7810.

Gebremichael, S., Birhanu, T., Tessema, D.A. (2012)

Analysis of organochlorine pesticide residues in human and cow's milk in the towns of Asendabo, Serbo and Jimma in South-Western Ethiopia.

Chemosphere, Article in Press.

Gerić, M., Ceraj-Cerić, N., Gajski, G., Vasilić, T., Capuder, T., Garaj-Vrhovac, V. (2012)

Cytogenetic status of human lymphocytes after exposure to low concentrations of p,p'-DDT, and its metabolites (p,p'-DDE, and p,p'-DDD) in vitro.

Chemosphere, 87 (11), pp. 1288-1294.

Giannandrea, F., Gandini, L., Paoli, D., Turci, R., Figà-Talamanca, I (2011)

Pesticide exposure and serum organochlorine residuals among testicular cancer patients and healthy controls.

Journal of environmental science and health. Part. B, Pesticides, food contaminants, and agricultural wastes, 46 (8), pp. 780-787.

Goldner, W. S., D. P. Sandler, F. Yu, V. Shostrom, J. A. Hoppin, F. Kamel and T. D. Levan (2013)

Hypothyroidism and Pesticide Use among Male Private Pesticide Applicators in the Agricultural Health Study.

Journal of Occupational and Environmental Medicine 55(10): 1171-1178.

Govarts, E., Nieuwenhuijsen, M., Schoeters, G., Ballester, F., Bloemen, K., de Boer, M., Chevrier, C., Eggesbø, M., Guxens, M., Krämer, U., Legler, J., Martínez, D., Palkovicova, L., Patelarou, E., Ranft, U., Rautio, A., Petersen, M.S., Slama, R., Stigum, H., Toft, G., Trnovec, T., Vandentorren, S., Weihe, P., Kuperus, N.W., Wilhelm, M., Wittsiepe, J., Bonde, J.P. (2012)

Birth weight and prenatal exposure to polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE): A meta-analysis within 12 European birth cohorts.

Environmental Health Perspectives, 120 (2), pp. 162-170.

Hernik, A., Góralczyk, K., Struciński, P., Czaja, K., Kucharska, A., Korcz, W., Snopczyński, T., Ludwicki, J.K. (2011)

Polybrominated diphenyl ethers, polychlorinated biphenyls and organochlorine pesticides in human milk as markers of environmental exposure to these compounds.

Annals of Agricultural and Environmental Medicine, 18 (1), pp. 113-118.

Herrero-Mercado, M., Waliszewski, S.M., Valencia-Quintana, R., Caba, M., Hernández-Chalate, F., García-Aguilar, E., Villalba, R. (2010)

Organochlorine pesticide levels in adipose tissue of pregnant women in Veracruz, Mexico.

Bulletin of Environmental Contamination and Toxicology, 84 (6), pp. 652-656.

Howell, G., Mangum, L. (2011)

Exposure to bioaccumulative organochlorine compounds alters adipogenesis, fatty acid uptake, and adipokine production in NIH3T3-L1 cells.

Toxicology in Vitro, 25 (1), pp. 394-402.

Hurd-Brown, T., Udoji, F., Martin, T., Whalen, M.M. (2013)

Effects of DDT and triclosan on tumor-cell binding capacity and cell-surface protein expression of human natural killer cells.

Journal of Applied Toxicology, 33 (6), pp. 495-502.

Imbeault, P., Findlay, C.S., Robidoux, M.A., Haman, F., Blais, J.M., Tremblay, A., Springthorpe, S., Pal, S., Seabert, T., Krümmel, E.M., Maal-Bared, R., Tetro, J.A., Pandey, S., Sattar, S.A., Fillion, L.G. (2012)

Dysregulation of cytokine response in Canadian first nations communities: Is there an association with persistent organic pollutant levels?

PLoS ONE, 7 (7), art. no. e39931.

Ingber, S. Z., M. C. Buser, H. R. Pohl, H. G. Abadin, H. Edward Murray and F. Scinicariello (2013). "DDT/DDE and breast cancer: A meta-analysis."

Regulatory Toxicology and Pharmacology 67(3): 421-433.

Johnson, N.A., Ho, A., Mark Cline, J., Hughes, C.L., Foster, W.G., Davis, V.L. (2012)

Accelerated mammary tumor onset in a HER2/neu mouse model exposed to DDT metabolites locally delivered to the mammary gland.

Environmental Health Perspectives, 120 (8), pp. 1170-1176.

Jusko, T.A., Klebanoff, M.A., Brock, J.W., Longnecker, M.P. (2012)

In-utero exposure to dichlorodiphenyltrichloroethane and cognitive development among infants and school-aged children.
Epidemiology, 23 (5), pp. 689-698.

Kamel, F., Umbach, D.M., Bedlack, R.S., Richards, M., Watson, M., Alavanja, M.C.R., Blair, A., Hoppin, J.A., Schmidt, S., Sandler, D.P. (2012)
Pesticide exposure and amyotrophic lateral sclerosis.
NeuroToxicology, 33 (3), pp. 457-462.

Kazantseva, Y.A., Yarushkin, A.A., Pustyl'nyak, V.O. (2013)
Dichlorodiphenyltrichloroethane technical mixture regulates cell cycle and apoptosis genes through the activation of CAR and ER α in mouse livers.
Toxicology and Applied Pharmacology, 271 (2), pp. 137-143.

Kezios, K.L., Liu, X., Cirillo, P.M., Cohn, B.A., Kalantzi, O.I., Wang, Y., Petreas, M.X., Park, J.-S., Factor-Litvak, P. (2013)
Dichlorodiphenyltrichloroethane (DDT), DDT metabolites and pregnancy outcomes.
Reproductive Toxicology, 35 (1), pp. 156-164.

La Merrill, M., Cirillo, P.M., Terry, M.B., Krigbaum, N.Y., Flom, J.D., Cohn, B.A. (2013)
Prenatal exposure to the pesticide DDT and hypertension diagnosed in women before age 50: A longitudinal birth cohort study.
Environmental Health Perspectives, 121 (5), pp. 594-599.

Leino, O., Kiviranta, H., Karjalainen, A.K., Kronberg-Kippilä, C., Sinkko, H., Larsen, E.H., Virtanen, S., Tuomisto, J.T. (2013)
Pollutant concentrations in placenta.
Food and Chemical Toxicology, 54, pp. 59-69.

Linderholm, L., Jakobsson, K., Lundh, T., Zamir, R., Shoeb, M., Nahar, N., Bergman, A. (2011)
Environmental exposure to POPs and heavy metals in urban children from Dhaka, Bangladesh.
Journal of Environmental Monitoring, 13 (10), pp. 2728-2734.

Liu, J., M. Zhao, et al. (2012).
Low Concentrations of o,p'-DDT Inhibit Gene Expression and Prostaglandin Synthesis by Estrogen Receptor-Independent Mechanism in Rat Ovarian Cells.
PLoS ONE 7(11).

Lopez-Espinosa MJ, Vizcaino E, Murcia M, Fuentes V, Garcia AM, Rebagliato M, Grimalt JO, Ballester F. (2010)
Prenatal exposure to organochlorine compounds and neonatal thyroid stimulating hormone levels.
Journal of Exposure Science and Environmental Epidemiology, 20 (7), pp. 579-588.

Lopez-Espinosa, M.-J., Murcia, M., Iñiguez, C., Vizcaino, E., Llop, S., Vioque, J., Grimalt, J.O., Rebagliato, M., Ballester, F. (2011)
Prenatal exposure to organochlorine compounds and birth size.
Pediatrics, 128 (1), pp. e127-e134.

- Luccio-Camelo, D.C., Prins, G.S. (2011)
Disruption of androgen receptor signaling in males by environmental chemicals.
Journal of Steroid Biochemistry and Molecular Biology, 127 (1-2), pp. 74-82.
- Mahalingaiah, S., Missmer, S.A., Maity, A., Williams, P.L., Meeker, J.D., Berry, K., Ehrlich, S., Perry, M.J., Cramer, D.W., Hauser, R. (2012)
Association of hexachlorobenzene (HCB), dichlorodiphenyl-trichloroethane (DDT), and Dichlorodiphenyldichloroethylene (DDE) with in vitro fertilization (IVF) outcomes.
Environmental Health Perspectives, 120 (2), pp. 316-320
- Martenies, S.E., Perry, M.J. (2013)
Environmental and occupational pesticide exposure and human sperm parameters: a systematic review.
Toxicology, 307, pp. 66-73.
- Masumo, R., Bårdsen, A., Åstrøm, A.N. (2013)
Developmental defects of enamel in primary teeth and association with early life course events: A study of 6-36 month old children in Manyara, Tanzania.
BMC Oral Health, 13 (1), art. no. 21.
- McAuliffe, M.E., Williams, P.L., Korrick, S.A., Altshul, L.M., Perry, M.J. (2012)
Environmental exposure to polychlorinated biphenyls and p,p'-DDE and sperm sex-chromosome disomy.
Environmental Health Perspectives, 120 (4), pp. 535-540.
- Mendez, M.A., Garcia-Esteban, R., Guxens, M., Vrijheid, M., Kogevinas, M., Goñi, F., Fochs, S., Sunyer, J. (2011)
Prenatal organochlorine compound exposure, rapid weight gain, and overweight in infancy.
Environmental Health Perspectives, 119 (2), pp. 272-278.
- Mercado, L.A., Freille, S.M., Vaca-Pereira, J.S., Cuellar, M., Flores, L., Mutch, E., Olea, N., Arrebola, J.P. (2013)
Serum concentrations of p,p'-dichlorodiphenyltrichloroethane (p,p'-DDE) in a sample of agricultural workers from Bolivia.
Chemosphere, 91 (10), pp. 1381-1385.
- Meza-Montenegro, M.M., Valenzuela-Quintanar, A.I., Balderas-Cortés, J.J., Yañez-Estrada, L., Gutiérrez-Coronado, M.L., Cuevas-Robles, A., Gandolfi, A.J. (2013)
Exposure assessment of organochlorine pesticides, arsenic, and lead in children from the major agricultural areas in Sonora, Mexico.
Archives of Environmental Contamination and Toxicology, 64 (3), pp. 519-527.
- Mishra, K., Sharma, R.C. (2011)
Assessment of organochlorine pesticides in human milk and risk exposure to infants from North-East India.

Science of the Total Environment, 409 (23), pp. 4939-4949.

Montes, L.P.B., Waliszewski, S., Hernández-Valero, M., Sanín-Aguirre, L., Infanzón-Ruiz, R.M., Jañas, A.G. (2010)
Prenatal exposure to organochlorine pesticides and cryptorchidism
[Exposición prenatal a los plaguicidas organoclorados y criptorquidia].
Ciencia e Saude Coletiva, 15 (SUPPL. 1), pp. 1169-1174.

Nelson, S., Albert, J.M., Geng, C., Curtan, S., Lang, K., Miadich, S., Heima, M., Malik, A., Ferretti, G., Eggertsson, H., Slayton, R.L., Milgrom, P. (2013)
Increased enamel hypoplasia and very low birthweight infants.
Journal of Dental Research, 92 (9), pp. 788-794.

Nicolle-Mir, L. (2012)
Fetal exposure to organochloride compounds and birth weight. Exposition
foetale aux organochlorés et poids de naissance.
Environnement, Risques & Santé 11, 343-344

Ociepa-Zawal, M., Rubis, B., Wawrzynczak, D., Wachowiak, R., Trzeciak, W.H. (2010)
Accumulation of environmental estrogens in adipose tissue of breast cancer patients.
Journal of Environmental Science and Health - Part A Toxic/Hazardous Substances and Environmental Engineering, 45 (3), pp. 305-312.

Ozcan, S., Tor, A., Aydin, M.E. (2011)
Levels of Organohalogenated Pollutants in Human Milk Samples from Konya City, Turkey.
Clean - Soil, Air, Water, 39 (10), pp. 978-983.

Persson, E.C., Graubard, B.I., Evans, A.A., London, W.T., Weber, J.-P., Leblanc, A., Chen, G., Lin, W., McGlynn, K.A. (2012)
Dichlorodiphenyltrichloroethane and risk of hepatocellular carcinoma.
International Journal of Cancer, 131 (9), pp. 2078-2084.

Pestana, D., Teixeira, D., Faria, A., Domingues, V., Monteiro, R., Calhau, C. (2013)
Effects of environmental organochlorine pesticides on human breast cancer: Putative involvement on invasive cell ability.
Environmental Toxicology. Article in Press.

Porpora, M.G., Lucchini, R., Abballe, A., Ingelido, A.M., Valentini, S., Fuggetta, E., Cardi, V., Ticino, A., Marra, V., Fulgenzi, A.R., De Felip, E. (2013)
Placental transfer of persistent organic pollutants: A preliminary study on mother-newborn pairs.
International Journal of Environmental Research and Public Health, 10 (2), pp. 699-711.

Raab, U., Albrecht, M., Preiss, U., Völkel, W., Schwegler, U., Fromme, H. (2013)
Organochlorine compounds, nitro musks and perfluorinated substances in breast milk - Results from Bavarian monitoring of breast milk 2007/8.

Chemosphere, 93 (3), pp. 461-467.

Rahman, M.M. (2013)

Insecticide substitutes for DDT to control mosquitoes may be causes of several diseases.

Environmental Science and Pollution Research, 20 (4), pp. 2064-2069.

Reid, A., Callan, A., Stasinska, A., Heyworth, J., Phi, D.T., Odland, J.O., Hinwood, A. (2013)

Maternal exposure to organochlorine pesticides in Western Australia.

Science of the Total Environment, 449, pp. 208-213.

Ren, A., Qiu, X., Jin, L., Ma, J., Li, Z., Zhang, L., Zhu, H., Finnell, R.H., Zhu, T. (2011).

Association of selected persistent organic pollutants in the placenta with the risk of neural tube defects.

Proceedings of the National Academy of Sciences of the United States of America, 108 (31), pp. 12770-12775.

Rignell-Hydbom, A., Elfving, M., Ivarsson, S.A., Lindh, C., Jönsson, B.A.G., Olofsson, P., Rylander, L. (2010)

A nested case-control study of intrauterine exposure to persistent organochlorine pollutants in relation to risk of Type 1 diabetes.

PLoS ONE 5(6): p. e11281. doi:10.1371/journal.pone.0011281

Rignell-Hydbom, A., Lindh, C. H. et al. (2012).

A Nested Case-Control Study of Intrauterine Exposure to Persistent Organochlorine Pollutants and the Risk of Hypospadias.

PLoS ONE, 7.

Ritter, R., Scheringer, M., MacLeod, M., Hungerbühler, K. (2011)

Assessment of nonoccupational exposure to DDT in the tropics and the north: Relevance of uptake via inhalation from indoor residual spraying.

Environmental Health Perspectives, 119 (5), pp. 707-712.

Rojas-Squella, X., Santos, L., Baumann, W., Landaeta, D., Jaimes, A., Correa, J.C., Sarmiento, O.L., Ramos-Bonilla, J.P. (2013)

Presence of organochlorine pesticides in breast milk samples from Colombian women.

Chemosphere, 91 (6), pp. 733-739.

Rudge, C.V.C., Sandanger, T., Röllin, H.B., Calderon, I.M.P. , Volpato, G., Silva, J.L.P., Duarte, G., Neto, C.M., Sass, N., Nakamura, M.U., Odland, J.O., Rudge, M.V.C. (2011).

Levels of selected persistent organic pollutants in blood from delivering women in seven selected areas of São Paulo State, Brazil.

Environment International, Article in Press.

Russell, T.L., Beebe, N.W., Cooper, R.D., Lobo, N.F., Burkot, T.R. (2013)

Successful malaria elimination strategies require interventions that target changing vector behaviours.

Malaria Journal, 12 (1), art. no. 56.

Sagiv, S.K., Thurston, S.W., Bellinger, D.C., Tolbert, P.E., Altshul, L.M., Korrick, S.A. (2010)
Prenatal organochlorine exposure and behaviors associated with attention deficit hyperactivity disorder in school-aged children.
American Journal of Epidemiology, 171 (5), pp. 593-601.

Sagiv, S.K., Thurston, S.W., Bellinger, D.C., Altshul, L.M., Korrick, S.A. (2012)
Neuropsychological measures of attention and impulse control among 8-year-old children exposed prenatally to organochlorines.
Environmental Health Perspectives, 120 (6), pp. 904-909.

Salazar, F.V., Achee, N.L., Grieco, J.P., Prabaripai, A., Ojo, T.A., Eisen, L., Dureza, C., Polsomboon, S., Chareonviriyaphap, T. (2013)
Effect of Aedes aegypti exposure to spatial repellent chemicals on BG-Sentinel™ trap catches.
Parasites and Vectors, 6 (1), art. no. 145

Sawada, N., Iwasaki, M., Inoue, M., Itoh, H., Sasazuki, S., Yamaji, T., Shimazu, T., Tsugane, S. (2010)
Plasma organochlorines and subsequent risk of prostate cancer in Japanese men: A nested case-control study.
Environmental Health Perspectives, 118 (5), pp. 659-665.

Sexton, K., Salinas, J.J., McDonald, T.J., Gowen, R.M.Z., Miller, R.P., McCormick, J.B., Fisher-Hoch, S.P. (2013)
Biomarkers of maternal and fetal exposure to organochlorine pesticides measured in pregnant hispanic women from brownsville, texas.
International Journal of Environmental Research and Public Health, 10 (1), pp. 237-248.

Sharaf, N. E., N. M. Amer, K. S. Ibrahim, E. M. El-Tahlawy and K. S. Abdelgelil (2013).
Pesticides usage in agriculture among rural women in Egypt: Association between serum organo-chlorine pesticide residues and occurrence of diabetes.
World Journal of Medical Sciences 9(1): 8-15.

Sharma, E., Mustafa, M., Pathak, R., Guleria, K., Ahmed, R.S., Vaid, N.B., Banerjee, B.D. (2012) (01)
A case control study of gene environmental interaction in fetal growth restriction with special reference to organochlorine pesticides.
European Journal of Obstetrics Gynecology and Reproductive Biology, 161 (2), pp. 163-169.

Sharma, S.K., Upadhyay, A.K., Haque, M.A., Tyagi, P.K., Kindo, B.K. (2012) (02)
Impact of changing over of insecticide from synthetic pyrethroids to DDT for indoor residual spray in a malaria endemic area of Orissa, India.
Indian Journal of Medical Research, 135 (3), pp. 382-388.

Shekharyadav, C., Bajpai, M., Kumar, V., Ahmed, R.S., Gupta, P., Banerjee, B.D. (2011)
Polymorphism in CYP1A1, GSTM1, GSTT1 genes and organochlorine pesticides in the etiology of hypospadias.

Human and Experimental Toxicology, 30 (10), pp. 1464-1474.

Shi, Y.-Q., Li, H.-W., Wang, Y.-P., Liu, C.-J., Yang, K.-D. (2013)
p, p'-DDE induces apoptosis and mRNA expression of apoptosis-associated
genes in testes of pubertal rats.
Environmental Toxicology, 28 (1), pp. 31-41.

Shrestha, S.K.a , Aulakh, R.S.b , Bedi, J.S.b , Gill, J.P.S.b (2011)
Monitoring of pesticide residues in human population of Nepal.
5th International Conference on Bioinformatics and Biomedical Engineering,
iCBBE 2011, art. no. 5781441

Singh, N.K., Chhillar, N., Banerjee, B.D., Bala, K., Basu, M., Mustafa, M.
(2013)
Organochlorine pesticide levels and risk of Alzheimer's disease in north
Indian population.
Human and Experimental Toxicology, 32 (1), pp. 24-30.

Sioen, I., Den Hond, E., Nelen, V., Van de Mieroop, E., Croes, K., Van
Larebeke, N., Nawrot, T.S., Schoeters, G. (2013)
Prenatal exposure to environmental contaminants and behavioural problems at
age 7-8 years.
Environment International, 59, pp. 225-231.

Smith, E., Weber, J., Rofo, A., Gancarz, D., Naidu, R., Juhasz, A.L. (2012)
Assessment of DDT relative bioavailability and bioaccessibility in
historically contaminated soils using an in vivo mouse model and fed and
unfed batch in vitro assays.
Environmental Science and Technology, 46 (5), pp. 2928-2934.

Smith-Bindman, R. (2012)
Environmental causes of breast cancer and radiation from medical imaging:
Findings from the Institute of Medicine report.
Archives of Internal Medicine, 172 (13), pp. 1023-1027.

Son, H.-K., Kim, S.-A., Kang, J.-H., Chang, Y.-S., Park, S.-K. , Lee, S.-
K., Jacobs, D.-R., Lee, D.-H. (2010)
Strong associations between low-dose organochlorine pesticides and type 2
diabetes in Korea.
Environment International, 36 (5), pp. 410-414.

Su, Y., Dai, Y., Lin, Y., Gao, X., Han, Y., Zhao, B. (2012)
Serum organochlorine pesticide residues and risk of gallstone disease: A
case-control study in Xiamen.
Annals of Epidemiology, 22 (8), pp. 592-597.

Sunyer, J. , Garcia-Esteban, R., Alvarez, M., Guxens, M., Goñi, F.,
Basterrechea, M., Vrijheid, M., Guerra, S., Antó, J.M. (2010)
DDE in mothers' blood during pregnancy and lower respiratory tract
infections in their infants.
Epidemiology, 21 (5), pp. 729-735.

Takakura, N., Sanders, P., Fessard, V., Le Hégarat, L. (2013)

In vitro combined cytotoxic effects of pesticide cocktails simultaneously found in the French diet.

Food and Chemical Toxicology, 52, pp. 153-162.

Tang-Péronard, J.L., Andersen, H.R., Jensen, T.K., Heitmann, B.L. (2011)
Endocrine-disrupting chemicals and obesity development in humans: A review.
Obesity Reviews, 12 (8), pp. 622-636.

Taylor, K.W., Novak, R.F., Anderson, H.A., Birnbaum, L.S., Blystone, C., De Vito, M., Jacobs, D., Köhrle, J., Lee, D.-H., Rylander, L., Rignell-Hydbom, A., Tornero-Velez, R., Turyk, M.E., Boyles, A.L., Thayer, K.A., Lind, L. (2013)

Evaluation of the association between persistent organic pollutants (POPs) and diabetes in epidemiological studies: A national toxicology program workshop review.

Environmental Health Perspectives, 121 (7), pp. 774-783.

Tetreau, G., Chandor-Proust, A., Faucon, F., Stalinski, R., Akhouayri, I., Prud'homme, S.M., Raveton, M., Reynaud, S. (2013)

Contrasting patterns of tolerance between chemical and biological insecticides in mosquitoes exposed to UV-A.

Aquatic Toxicology, 140-141, pp. 389-397.

Toft, G., Thulstrup, A.M., Jönsson, B.A., Pedersen, H.S., Ludwicki, J.K., Zvezday, V., Bonde, J.P. (2010)

Fetal loss and maternal serum levels of 2,2',4,4',5,5'-hexachlorobiphenyl (CB-153) and 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (p,p'-DDE) exposure: A cohort study in Greenland and two European populations.

Environmental Health: A Global Access Science Source, 9 (1), art. no. 22.

Tomita, M., T. Yoshida, J. Fukumori, S. Yamaguchi, S. Kojima, T. Fukuyama, A. Ohnuma-Koyama, N. Takahashi, Y. Takeuchi-Kashimoto, M. Kuwahara, N. Nakashima, R. Ohtsuka, M. Takeda, T. Kosaka and T. Harada (2013).

p, p'-DDT induces microcytic anemia in rats.

Journal of Toxicological Sciences 38(5): 775-782.

Torres-Sánchez, L., Schnaas, L., Rothenberg, S.J., Cebrián, M.E., Osorio-Valencia, E., Del Carmen Hernández, M., García-Hernández, R.M., López-Carrillo, L. (2013)

Prenatal p,p'-DDE exposure and neurodevelopment among children 3.5-5 years of age.

Environmental Health Perspectives, 121 (2), pp. 263-268.

Trejo-Acevedo, A., Rivero-Pérez, N.E., Flores-Ramírez, R., Orta-García, S.T., Varela-Silva, J.A., Pérez-Maldonado, I.N. (2012)

Assessment of the levels of persistent organic pollutants and 1-hydroxypyrene in blood and urine samples from Mexican children living in an endemic malaria area in Mexico.

Bulletin of Environmental Contamination and Toxicology, 88 (6), pp. 828-832.

Ukropec, J., Radikova, Z., Huckova, M., Koska, J., Kocan, A., Sebkova, E., Drobna, B., Trnovec, T., Susienkova, K., Labudova, V., Gasperikova, D., Langer, P., Klimes, I. (2010)

High prevalence of prediabetes and diabetes in a population exposed to high levels of an organochlorine cocktail.
Diabetologia, 53 (5), pp. 899-906.

Valera, B., Ayotte, P., Poirier, P., Dewailly, T. (2013a)
Associations between plasma persistent organic pollutant levels and blood pressure in Inuit adults from Nunavik.
Environment International, 59, pp. 282-289.

Valera, B., Jørgensen, M.E., Jeppesen, C., Bjerregaard, P. (2013b)
Exposure to persistent organic pollutants and risk of hypertension among Inuit from Greenland.
Environmental Research, 122, pp. 65-73.

Valvi, D., Mendez, M.A., Martinez, D., Grimalt, J.O., Torrent, M., Sunyer, J., Vrijheid, M. (2012)
Prenatal concentrations of polychlorinated biphenyls, DDE, and DDT and overweight in children: A prospective birth cohort study.
Environmental Health Perspectives, 120 (3), pp. 451-457.

Viel, J.-F., Floret, N., Deconinck, E., Focant, J.-F., De Pauw, E., Cahn, J.-Y. (2011)
Increased risk of non-Hodgkin lymphoma and serum organochlorine concentrations among neighbors of a municipal solid waste incinerator.
Environment International, 37 (2), pp. 449-453.

Vukavić, T., Vojinović Miloradov, M., Mihajlović, I., Ristivojević, A. (2013)
Human milk POPs and neonatal risk trend from 1982 to 2009 in the same geographic region in Serbia.
Environment International, 54, pp. 45-49.

Waliszewski, S.M., Caba, M., Herrero-Mercado, M., Saldariaga-Noreña, H., Meza, E., Zepeda, R., Martínez-Valenzuela, C., Infanzon, R., Hernández-Chalate, F. (2011)
Monitoring of organochlorine pesticide residue levels in adipose tissue of Veracruz, Mexico inhabitants.
Bulletin of Environmental Contamination and Toxicology, 87 (5), pp. 539-544.

Waliszewski, S.M., Caba, M., Herrero-Mercado, M., Saldariaga-Noreña, H., Meza, E., Zepeda, R., Martínez-Valenzuela, C., Arroyo, S.G., Pietrini, R.V. (2012) (01)
Organochlorine pesticide residue levels in blood serum of inhabitants from Veracruz, Mexico.
Environmental Monitoring and Assessment, 184 (9), pp. 5613-5621.

Waliszewski, S.M., Caba, M., Rodríguez Díaz, S.S., Saldarriaga-Noreña, H., Meza, E., Zepeda, R., Infanzón, R. (2012) (02)
Levels of Organochlorine Pesticides Residues in Human Adipose Tissue, Data from Tabasco, Mexico.
Bulletin of Environmental Contamination and Toxicology, pp. 1-6. Article in Press.

- Waliszewski, S.M., Sanchez, K., Caba, M., Saldariaga-Noreña, H., Meza, E., Zepeda, R., Valencia Quintana, R., Infanzon, R. (2012) (03)
Organochlorine pesticide levels in female adipose tissue from Puebla, Mexico.
Bulletin of Environmental Contamination and Toxicology, 88 (2), pp. 296-301
- Wang, N., Shi, L., Kong, D., Cai, D., Cao, Y., Liu, Y., Pang, G., Yu, R. (2011)
Accumulation levels and characteristics of some pesticides in human adipose tissue samples from Southeast China
Chemosphere, 84 (7), pp. 964-971.
- Wang, H.-S., Chen, Z.-J., Wei, W., Man, Y.-B., Giesy, J.P., Du, J., Zhang, G., Wong, C.K.C., Wong, M.-H. (2013a)
Concentrations of organochlorine pesticides (OCPs) in human blood plasma from Hong Kong: Markers of exposure and sources from fish.
Environment International, 54, pp. 18-25.
- Wang, W., Huang, M.-J., Wu, F.-Y., Kang, Y., Wang, H.-S., Cheung, K.C., Wong, M.H. (2013b)
Risk assessment of bioaccessible organochlorine pesticides exposure via indoor and outdoor dust.
Atmospheric Environment, 77, pp. 525-533.
- Warner, M., Schall, R.A., Harley, K.G., Bradman, A., Barr, D., Eskenazi, B. (2013)
In utero DDT and DDE exposure and obesity status of 7-year-old Mexican-American children in the CHAMACOS cohort.
Environmental Health Perspectives, 121 (5), pp. 631-636.
- Wassie, F., Spanoghe, P., Tessema, D.A., Steurbaut, W. (2012)
Exposure and health risk assessment of applicators to DDT during indoor residual spraying in malaria vector control program.
Journal of Exposure Science and Environmental Epidemiology, . Article in Press.
- Watanabe, M.X., Kunisue, T., Ueda, N., Nose, M., Tanabe, S., Iwata, H. (2013)
Toxicokinetics of dioxins and other organochlorine compounds in Japanese people: Association with hepatic CYP1A2 expression levels.
Environment International, 53, pp. 53-61.
- Wielgomas, B., Czarnowski, W., Jansen, E.H.J.M. (2012)
Persistent organochlorine contaminants in hair samples of Northern Poland population, 1968-2009.
Chemosphere, 89 (8), pp. 975-981.
- Wojtyniak, B.J., Rabczenko, D., Jonsson, B.A.G., Zvezday, V., Pedersen, H.S., Rylander, L., Toft, G., Ludwicki, J.K., Goralczyk, K., Lesovaya, A., Hagmar, L., Bonde, J.P. (2010)
Association of maternal serum concentrations of 2,2' , 4,4' 5,5' - hexachlorobiphenyl (CB-153) and 1,1-dichloro-2,2-bis (p-chlorophenyl)-ethylene (p,p'-DDE) levels with birth weight, gestational age and preterm births in Inuit and European populations.

Environmental Health: A Global Access Science Source, p. 56. Article in Press.

Yamazaki, H., Takano, R., Horiuchi, K., Shimizu, M., Murayama, N., Kitajima, M., Shono, F. (2010)
Human blood concentrations of dichlorodiphenyltrichloroethane (DDT) extrapolated from metabolism in rats and humans and physiologically based pharmacokinetic modeling.
Journal of Health Science, 56 (5), pp. 566-575.

Young, S.-C., Chang, L.W., Lee, H.-L., Tsai, L.-H., Liu, Y.-C., Lin, P. (2010)
DNA damage induced by trans, trans-2,4-decadienal (tt-DDE), a component of cooking oil fume, in human bronchial epithelial cells.
Environmental and Molecular Mutagenesis, 51 (4), pp. 315-321.

Zhao BA, Shen HB, Liu FB, Liu SA, Niu JC, Guo FA, Sun XD (2011)
Exposure to organochlorine pesticides is independent risk factor of hepatocellular carcinoma: A case-control study.
J Expo Sci Environ Epidemiol. **21**(6):601-8.

Zhuang, S.a , Zhang, J.a , Wen, Y.a , Zhang, C.b , Liu, W.a (2012)
Distinct mechanisms of endocrine disruption of DDT-related pesticides toward estrogen receptor α and estrogen-related receptor γ .
Environmental Toxicology and Chemistry, 31(11):2597-605.